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REPORT
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EXPEDITION
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1900

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REPORT OF THE YELLOW FEVER EXPEDITION TO PARÀ

SEPTEMBER, 1901

LIVERPOOL SCHOOL OF TROPICAL MEDICINE—MEMOIR VII

REPORT

OF THE

YELLOW FEVER EXPEDITION TO PARÀ

OF THE

LIVERPOOL SCHOOL OF TROPICAL MEDICINE
AND MEDICAL PARASITOLOGY

BY

H. E. DURHAM

WITH ILLUSTRATIONS AND PLATE

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CONTENTS

		PAGE
Chapter I.	PREFACE	1
Chapter II.	PRELIMINARY THOUGHTS ON THE PROBLEM OF THE ETIOLOGY OF YELLOW FEVER	3
Chapter III.	PRELIMINARY REPORT (reprinted from *British Medical Journal*)	5
	INTERIM REPORT „ „ „	8
Chapter IV.	RECENT OBSERVATIONS ON YELLOW FEVER ETIOLOGY—	
	A. SANARELLI'S Bacillus . . .	10
	B. Mosquito Transference . . .	15
Chapter V.	OWN OBSERVATIONS ON YELLOW FEVER ETIOLOGY .	26
Chapter VI.	NOTES ON POINTS CONNECTED WITH YELLOW FEVER—	
	A. 'Typical Bites'	34
	B. Lymphatic Glands . . .	35
	C. Urine	38
	D. Kidney, Spleen, etc.	40
	E. Illness at the Instituto Lauro Sodré, and our own Infection	42
	F. Yellow Fever on Ships . . .	46
Chapter VII.	NOTES ON AGUE AT PARA, etc. . . .	50
Chapter VIII.	NOTES ON GENERAL HEALTH AT PARA . .	58
Chapter IX.	ODD NOTES. (*A*) PRICKLY HEAT. (*B*) DREPANIDIUM, etc.	75

REPORT OF AN EXPEDITION TO PARÀ, BRAZIL, TO STUDY YELLOW FEVER

8 . 1 . 03 .

PREFACE

The sad loss of my comrade, WALTER MYERS, after some nine months of constant companionship, though already engraved on the records of scientific research and adventure, cannot be passed over in silence. Shortly before we were struck, almost simultaneously, with the fever, we had agreed to confine our attention to a short programme, which would possibly have allowed us to return home some two months later. This, however, was not to be. The defects of this report will be a tribute to the lack of his friendly criticism, and the omissions would have been observations nearer

ERRATA

P. 15, in footnote. For 'SCHWALBS' read 'SCHWALBE.'
P. 19, in footnote. For '*Aufklärung*' read '*Aufklärung.*'
P. 44, chart opposite, in Case 1. For 'Nov.' read 'SEP.'

apparatus, which had arrived some two weeks before us, and which eventually was liberated on September 13. We were able to obtain fifteen autopsies on yellow fever cadavers up to January 15, when work was interrupted by our own infection. After my return, on February 15, the prevalence of the fever had diminished so much that

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A more pleasurable task is to record the appreciation of, and gratitude to, those from whom we received assistance in the furthering of our aims. First and foremost is due our thanks to Dr. José PAES DE CARVALHO, whose constant solicitude for our welfare, both in health and sickness, and whose position as the worthy Governor of the State of Parà rendered the prosecution of our researches possible.

To Dr. PONTES DE CARVALHO, Director of the Hospital Domingos Freire, which is reserved for the treatment of yellow fever patients, is due our thanks for allowing us all facilities in obtaining material from the cases under his charge. Dr. FRANCISCO MIRANDA, of the Sanitary Service, and several of the doctors in charge of the hospitals afforded us aid.

Mr. C. L. TEMPLE (Acting British Consul), Mr. BEALE (of Messrs. Singlehurst, Brocklehurst & Co.), and Captain CRIMP and Mr. COLLARD (of Messrs. Booth & Co.) also lent us their aid, often, be it said, at much personal inconvenience; we were much indebted to these gentlemen for their invaluable help.

Arriving in Parà on August 24, 1900, we were unable to commence for some weeks owing to the hebetude of the Custom House officials in the release of our apparatus, which had arrived some two weeks before us, and which eventually was liberated on September 13. We were able to obtain fifteen autopsies on yellow fever cadavers up to January 15, when work was interrupted by our own infection. After my return, on February 15, the prevalence of the fever had diminished so much that

cases which came into the fever hospital were few and far between, and only two further autopsies were obtainable. The difficulty of obtaining material, which had been our chief obstacle all through, owing to the absence of any system of control or notification and isolation, now became so great that it was not thought expedient to continue.

Having ascertained that there was no use in proceeding to Havana, it was judged best to return home; but I must here express my thanks to Surgeon-General STERNBERG and Major REED for their kind offices. I have also to thank the Sanitary Officers in Jamaica and British Guiana for kindly and courteously replying to my enquiries. Mr. THEOBALD has kindly identified the mosquitoes collected.

II. PRELIMINARY THOUGHTS ON THE PROBLEM OF THE ETIOLOGY OF YELLOW FEVER

Before setting out upon such a mission as that of the investigation of the etiology of yellow fever, it was necessary to frame a sort of programme of the possibilities and the modes to be adopted in dealing with the same.

At the outset it appeared that the true infective agent of yellow fever has as yet escaped recognition. Though yellow fever is by no means a virgin field for investigation, there has been little or no agreement between different observers, in regard to their respective claims. The writings of some authors hardly give evidence that their methods were sufficient or accurate enough to be of value.

The study of yellow fever must be begun again from the commencement, and any organism which may be found will not only have to be constantly found, but it will also have to afford an explanation why it has escaped the attention of other observers. That a yellow fever microbe exists there can be no question. Whether it be protozoal or bacterial in nature, it will be necessary to endeavour to define the mode of transmission and its mode of life in the outer world. The possibilities which may be encountered with either a protozoal or bacterial parasite, suggest a number of themes for consideration.

By prejudice there may be an inclination to feel that either kind of parasite may be involved. The epidemiology of the disease (prel. note) is suggestive of the action of an intermediary transmitting agency; this perhaps might better have been referred to as a transmitting *agent* rather than as an intermediate *host*.

In the light of our knowledge of other diseases due to animal parasites, it is highly suggestive that this form of parasite would occur; the apparent limitation of the geography of the disease is likewise suggestive, but though no lasting and endemic hold has been taken in northern climes, the inability to do so has possibly been rather overrated by writers of text-books.

On the other hand, the onset and features of the disease, its rapid course and the subsequent immunity are all more in accordance with our knowledge of bacterial diseases. While granting that we know comparatively little of diseases due to protozoal parasites, the hope would rather be for the establishment of a bacillary agent which might offer the opportunity for therapeutic treatment (as by an antitoxin); on the other hand, *a priori* none such would be likely for a protozoal disease in which treatment as yet is based on mere empiricism.

In hunting for protozoal parasites, experience with the parasite of Tsetse disease and of malarial fever should prove useful. It will be necessary to search everything in the fresh state—blood at various stages of the disease, and the organs as soon after death as possible. As with the Tsetse parasite the centrifuge may be useful in separating the protoplasmic structures in the blood from the heavier red blood corpuscles.

For stained specimens careful fixation with formaldehyde and osmic vapour must be practised, and a variety of staining methods—'Romanowsky,' haematoxylin, acidified basic stains, etc,—tried. Lastly, any odd or unfamiliar object must be sketched and its size determined. At autopsies it will be necessary to examine the probable paths of infection ; that is to say, the superficial lymph glands in various regions. Should events guide satisfactorily it will be necessary to examine possible intermediary agents such as gnats.

Several considerations have to be borne in mind in enquiring into a 'new' disease from the bacterial point of view. In the first place the gross lesions, especially those of the liver in yellow fever, give no probability that the bacterium is especially localized in these parts; for instance, a very small amount of the botulismus toxin is sufficient to produce most intense fatty change in the liver, provided the animal lives long enough. This time factor is a consideration which apparently has not entered the minds of experimenters who have endeavoured to reproduce yellow fever in animals, it is unlikely that the lesions could be produced when a period of twenty-four to forty-eight hours only elapses between inoculation and death. In making experiments on animals it will be necessary to gauge the doses to allow the animal to survive several days.

It is unlikely that a highly septicaemic condition or that large numbers of bacteria become localised in the tissues (as in plague) otherwise it is difficult to understand why such bacterium has hitherto defied recognition. The two bacterial diseases which seem to be most apt for analogy, or the pathology of which might be kept to the fore, are botulismus and tetanus. In the former VAN ERMENGEN only succeeded in getting very few colonies of living bacilli from the organs of the fatal cases; but whilst he thus proved that actual infection had taken place he was able to reproduce the disease by absorption of toxin through the alimentary canal. Tetanus is also not particularly encouraging, for, with a scarcely discoverable number of individual bacilli, fearful havoc is wrought by intoxication. What has been already written in regard to paths of infection in a protozoal disease can only be reiterated for a bacillary one; it may be that in or about the site of primary infection it may be more easy to discover an organism, or, by examining the bottom of centrifugalized material. In the symptoms as described there does not appear to be much that suggests localizing—the vomiting, kidney and liver mischief might be purely toxic. On the other hand, pain in the epigastrium, upon which some authors lay much stress, is suggestive of some lesion possibly due to special localization.

It is not likely that the supposed bacterium will thrive on ordinary media, it might be, however, that insufficiently large proportions of tissue have been taken. This will apply to anaerobic as well as aerobic trials.

As general routine it will be sufficient to use liquid broth cultures in the first instance; any organisms that should grow freely must be found in pure condition (by observation and plating) ere it can be granted an etiological position.

Lastly, it must be remembered that a bacterium may produce very different effects according to the mode by which it is introduced into the system. (Compare experimental inoculation of animals with certain bacteria).

III. REPORTS

A. Preliminary Report[1]

Notwithstanding the acumen and the number of those who have attacked the question of the prevalence of yellow fever, much mystery and uncertainty still enshroud the epidemiology of the disease. The etiology, also, is not yet determined with certainty; the claim of Sanarelli that his so-called '*Bacillus icteroides*' is the true cause of yellow fever has not found favour with several workers who have made search in this direction. By the kind invitation of Dr. Sternberg, Surgeon-General of the U.S. Army, we had the opportunity of conferring with the commission (Drs. Reed, Carroll and Lazear) appointed by him to study the question in Cuba. We may here express our gratitude to these gentlemen for the most kind and courteous reception that they extended towards us, as well as to Major Gorgas (U.S. Army), the head of the bureau of inspection of infectious diseases in the city of Havana. We also had the pleasure and advantage of meeting Dr. Carter (of the U.S. Maine Hospital Service), Dr. Guiteras (now Professor in the Havana School of Tropical Diseases), Dr. Finlay, and Drs. Bango and Martinez (practitioners in the city).

Amongst the many conflicting opinions and statements concerning the disease it appears certain that neither the handling of or contact with yellow fever patients nor the performance of necropsies is capable *per se* of conveying the disease to non-immunes. It also appears probable that general ship's cargoes and the fomites of patients are also not directly infective; here, however, the evidence is not conclusive, and the present quarantine regulations require disinfection of all clothes and personal effects before they may be introduced into the United States.

It seems to be fairly definitely established that a yellow-fever patient may become a danger by 'infecting the house' in which he is placed. Given that a house is 'infected,' a visit by a non-immune person entails considerable risk of contracting the malady. It is alleged by some that visits made at night are more dangerous than those made during the daytime; but here the evidence is not very clear, and is more of the nature of an opinion. The nature of the essential factor present in an 'infected house' is as yet mysterious. One house after another in a street may become 'infected' without any apparent intercommunication of the inmates; the infection may skip over one or more houses and reappear at some distance. There are those who are bold enough to predict in a village that such and such a house will yield one or more cases of the fever on or about a certain day; and, naturally, they claim to be true prophets.

1. Reprinted from *British Medical Journal.*

Of the interesting and important facts which have been ascertained, those elucidated by Dr. CARTER in his study of outbreaks at Orwood, and TAYLOR (Miss) in 1898, are second to none.[1] The conditions were such that the intervals between the introduction of 'infecting' cases and the onset of secondary cases could be followed with accuracy. Dr. CARTER finds that an interval of about fourteen to twenty-one days obtains before the first secondary cases occur. The house is then in an 'infected' condition, and exposure for a few hours (for example, in one case four hours and a half) can lead to infection, with the incubation interval up to the normal four or five days. This was exemplified to us by the history of a case at Quemados, for which we are indebted to Dr. REED. In a house which had been occupied by non-immune officers all last year, two cases of yellow fever occurred this summer; one of these was unfortunately fatal. However, a male and a female nurse who had been occupied in tending the patients did not acquire the disease until about a fortnight after the death occurred. Other sources of infection could be excluded in these cases. No further cases occurred, as the house was cleared and liberally treated with perchloride. The slight epidemic, however, spread to other houses down the street, although they were detached and surrounded by a small amount of garden space.

This curious and somewhat prolonged interval is suggestive of a development of the infecting factor in or about some agent or matter in the domicile. What may be the nature of this supposed agent is not yet demonstrated, but the suggestion propounded by Dr. C. FINLAY, of Havana, some twenty years ago, that the disease was spread by means of mosquitoes hardly appears so fanciful in the light of recent discoveries in ague convection as appeared in the days when the idea was first broached. Dr. FINLAY's hypothesis is able to account for several curious points which obtain with yellow fever. Thus the limitation of the disease to the 'yellow fever zone,' where frost is unknown, the coincidence of yellow fever and rainy seasons, the cessation of the disease when the temperature falls below a certain point, and its non-recrudescence in an infected locality after a frost, are all compatible with an agency, such as a gnat, which becomes too sluggish to bite, or indeed which dies out in unfavourable climatic conditions. Such a theory also explains the curious spread of the disease from house to house, which has already been referred to. Another point is that the sanitary condition of a house may be good, and yet it may be severely 'infected.' An example of this was shown by the case of one of the leading hotels in Havana, of good sanitary repute, but the source of many fever cases this summer. The above sketch will suffice to show that some means of transmission by the aid of an intermediate host—a town-loving host for this town-loving disease—is to some extent more plausible than might be anticipated. Whether that hypothetical host is of the nature of a gnat remains unknown.

1. *New Orleans Medical and Surgical Journal*, May, 1900

It is commonly stated that one attack of the fever confers a long and lasting immunity against further attacks. The completeness of this immunity, however, is called in question by the cases which we had the opportunity of seeing. Thus out of the two or three dozen cases we saw, no fewer than four were reputed to have had previous attacks ; the previous attacks were not believed in as genuine yellow fever by those physicians who accept a rigid immunity as the fact. A few words may be said of one of these cases as illustrative of several points :—

> 'A lady had an attack of yellow fever in New Orleans, at the age of nineteen, in 1866 ; her account of the symptoms she experienced, and the fact that her sister had a "typical" attack at the same time tend to the conclusion that the illness was indeed yellow fever. Last year she was occupied as an "immune" in nursing yellow fever cases in Cuba during July and August, and then remained in the outskirts of Havana (Cerro) for the winter and spring. This summer she went to live in an insanitary house close to the hotel we have already alluded to as an infected house, situated in an "infected" neighbourhood. She soon contracted an illness of the nature of which there could be no doubt—a severe and prolonged attack of yellow fever.'

But our knowledge of infectious diseases all goes to show that a complete and absolute immunity is never acquired by a single attack, though second attacks are usually of a comparatively mild, or at any rate recoverable, type.

The coloured people and natives are also supposed to escape the disease, but we are informed that this is a statement which is not true, although so frequently repeated in text-books. We were lucky enough to see one negro during the course of a typical attack. The Cubans and the Cuban doctors are in the habit of asserting that the Cuban system is not capable of having yellow fever. It appears, however, that they are not unknown to suffer from a disease called 'borras.' Clinically 'borras' is like yellow fever—sometimes with black vomit and death with suppression of urine ; pathologically the lesions of yellow fever are said to be present in fatal cases. The Cubans also suffer and die from 'pernicious malarial fever,' the symptomatology and pathological anatomy of which are very suggestive of yellow fever. We were informed that the Cuban children frequently suffer from mild attacks of fever, which our informants believe are really mild attacks of yellow fever, and which give a comparative immunity in after-life.

It has already been mentioned that a sojourn of a non-immune for some hours in an infected house is very likely to lead to an attack ; and that this is supposed to be especially the case at night. Since many of the cases we saw were soldiers, their movements could be traced to some extent, and in more than one instance there was evidence of a single exposure after breaking bounds for a single night. Similar experiences are told of ship's crews under similar circumstances ; another example is to be found in the case of one hundred American military prisoners who were confined

in a barrack in which there had been several hundred deaths through yellow fever during the previous year of Spanish occupation ; none of these prisoners acquired the disease, but some twenty-five of their custodians fell ill or died of the fever.

Through the courtesy of Major GORGAS we were enabled to see the distribution of the fatal cases of yellow fever in the city for the past ten years. In these it was rather striking that the more disreputable quarters of the town were free from deaths from this cause. Immigrant women are few, and presumably the inhabitants are all 'immunes ;' still it is not improbable that the infective agent is harboured amongst them.

These few notes on some epidemiological points are submitted in the hope that they may be of some interest to students of the perplexing questions and of the unravelled natural history of yellow fever.

B. ABSTRACT OF INTERIM REPORT[1]

1. Sufficient search reveals the presence of a fine, small bacillus in the organs of all fatal cases of yellow fever. We have found it in each of the fourteen cadavers examined for the purpose. In diameter the bacillus somewhat recalls that of the Influenza bacillus ; as seen in the tissues it is about 4 μ in length.

2. This bacillus has been found in kidney, in spleen, in mesenteric, portal, and axillary[2] lymphatic glands, etc., taken from yellow fever cadavers directly after death. In the contents of the lower intestine apparently the same bacillus is found, often in extraordinary preponderance over other micro-organisms. Preparations of the pieces of 'mucus,' which are usually if not always present in yellow fever stools, at times may almost present the appearance of 'pure culture.'

3. Preparations of the organs usually fail to show the presence of any other bacteria, whose absence is confirmed by the usual sterility of cultivation experiments.

4. It is probable that this same bacillus has been met with, but not recognized, by three other observers. Dr. STERNBERG[3] has mentioned it ; and he has also recorded the finding of similar organisms in material derived from Drs. DOMINGOS FREIRE and CARMONA Y VALLE, but he did not recognize its presence frequently, probably on account of the employment of insufficiently stringent staining technique.

5. It is probable that recognition has not been previously accorded to this bacillus by reason of the difficulty with which it takes up stains (especially methylene blue), and by reason of the difficulty of establishing growths on artificial media.

1. The completion of the interim report of which this is an abstract was interrupted by the onset of attacks of yellow fever in both of us. The loss of my much lamented colleague renders it advisable to submit this shortened report only for the time being.—H.E.D.

2. We find these constantly enlarged and much injected, though whether this is specific we are not able to say

3. Report on Etiology and Prevention of Yellow Fever, 1890.

6. The most successful staining reagent is carbol fuchsin solution (ZIEHL), diluted with 5 per cent. phenol solution (to prevent accidental contamination during the long staining period); immersion for several hours, followed by differentiation in weak acetic acid. Two hours staining period may fail to reveal bacilli, which appear after twelve to eighteen hours. The bacilli in the stools are often of greater length than those in the tissues, and they may stain rather more easily; naturally the same is true of cultures.

7. Since the bacilli are small and comparatively few in numbers, they are difficult to find. To facilitate matters at our last two autopsies (14th and 15th), a method of sedimentation has been adopted. A considerable quantity of organ juice is emulsified with antiseptic solutions, minute precautions against contamination, and for control being taken; the emulsion is shaken from time to time and allowed to settle. The method is successful and may form a ready means of preserving bacteria—containing material for future study. The best fluid for the purpose has yet to be worked out; hitherto normal saline with about one-fifth per cent. sublimate has been employed.

8. Pure growths of these bacilli are not obtained in ordinary aerobic and anaerobic culture tubes.

9. Some pure cultures have been obtained by placing whole mesenteric glands (cut out by means of the thermocautery) into broth under strict hydrogen atmosphere. Investigation into the necessary constitution of culture media for successful cultivation is in progress.

10. Much search was made for parasites of the nature of protozoa. We conclude that yellow fever is not due to this class of parasite. Our examinations were made on very fresh organ-juices, blood, etc., taken at various stages of the disease, with and without centrifugalizations,[1] and on specimens fixed and stained in appropriate ways. We may add that we have sometimes examined the organs in the fresh state under the microscope within half an hour of death.

11. The endeavour to prove a *man-to-man* transference of yellow fever by means of a particular kind of gnat by the recent American Commission, is hardly intelligible for a bacillary disease. Moreover, it does not seem to be borne out by their experiments, nor does it appear to satisfy certain endemiological conditions. It is proposed to deal more fully with the endemiology and epidemiology of the disease on a later occasion.

12. We think that the evidence in favour of the etiological importance of the fine small bacillus is stronger than any that has yet been adduced for any other pretended 'yellow fever germ.' At the same time there is much further work to be done ere its final establishment can be claimed. The acquisition of a new intestinal bacterium would explain the immunity of the 'acclimatized.'

1. We have found this sometimes useful in examining the blood of ague patients.

IV. RECENT OBSERVATIONS ON YELLOW FEVER ETIOLOGY

A. Sanarelli's bacillus

Sanarelli[1] claimed from the examination of twelve cases of yellow fever that he had established the etiology of the disease. He claims to have found his *B. icteroides* seven times, that is to say, in more than half of the cases. An examination of his account shews that much contamination with a variety of bacteria was met with, in fact, it was only from two cases that pure results were obtained, whilst in five cases it was not met with at all. The cases may be summarized shortly:—

Case 1	Autopsy	18 hrs.	after death	Variety of bacteria; no *B. icteroides* .	= o
„ 2	„	2	„	Pure *B. icteroides*	= +
„ 4	During life (liver and finger blood)			—*B. icteroides* and another species	= ?
„ 5	Autopsy	8 hrs.	after death	—Variety of bacteria, including *B. icteroides*	= ?
„ 6	„	3	„	Very abundant *B. coli*; no *B. icteroides* .	= o
„ 7	„	o	„	*Streptococci*; no *B. icteroides* . .	= o
„ 8	„	2	„	*Staphylococcus* and *B. icteroides* . . (During life, pure *B. icteroides* from finger blood, liver, and bile)	= +
„ 9	„	8	„	Mostly sterile, small undetermined bacillus, and one tube of pure *B. icteroides*	= ?
„ 10	„	6	„	Variety of bacteria; *B. icteroides* not found	= o
„ 11	„	o	„	*Staphylococci* and a bacillus which was identified as *B. icteroides*; the account is hardly satisfactory . . .	= ?
„ 12	„	6	„	Mostly sterile; a chicken cholera-like bacillus, and also a not very clear account of a bacillus identical with *B. icteroides*, which soon died out .	= ?
„ 13	„	o	„	*B. coli* and *Staphylococci*; no *B. icteroides*	= o

In total—two positive, five doubtful, and five negative cases, a result which is, perhaps, hardly sufficient for establishing the etiology of the disease. Moreover, the study of the characters of the bacillus does not impress the reader that the same bacillus was always met with; at any rate, a considerable amount of stress is laid upon the appearance of certain colonies upon agar, which alone, without other tests, is hardly sufficient as a criterion.

1. Sanarelli, *Annales de l'Institut Pasteur*, XI, 1887, pp. 433 and 673.

Following SANARELLI came a number of publications dealing with the bacillus; of these, that of WASDIN and GEDDINGS[1] gives positive finding of *B. icteroides* in thirteen out of fourteen cases examined. Whilst they undoubtedly met with the bacillus in question, their account, especially of the fermentation reactions, is not entirely clear; it is not possible to summarize their results, for it is not always certain whether the cultures mentioned were pure or not; in several instances it is stated that contaminations such as *B. coli* were present.

The much discussed case of P. Smith[2] perhaps gives a clue to the asserted frequency of occurrence of *B. icteroides*, 'the present attack of illness came on the 5th of February, 1899 (W. and G.).' On the 10th, *i.e.*, 'on the sixth day of the disease,' blood was taken from the ear tip, and with this plates were prepared; these 'gave us numerous colonies of *B. icteroides*; also of two other organisms, one a colon. We offered this evidence as diagnostic on the 12th.' It is not stated whether fermentation tests were made to prove the diagnosis of *B. icteroides* within this space of two days, anyhow it would not have been possible to have repeated them. At the autopsy 'in *twenty-four hours* the spleen gave a pure culture of *B. icteroides*, and the blood, a culture but slightly contaminated. Other organs and fluids the same. There was observed no *B. typhosus*.'

AGRAMONTE[3] does not regard this as a case of yellow fever at all; his account of it is at variance in several particulars; thus on February 4, P. Smith had 'felt sick for about a week,' or Major DUCKER's statement, 'on February 9, 1899. . . . . It was then the eighth day of the soldier's illness.' It is agreed that *B. icteroides* was present; thus, 'We found *B. typhosus* and *B. icteroides* in almost pure cultures from the spleen; *B. typhosus* in pure culture from the kidney; *B. coli*, *B. icteroides*, and a non-motile bacillus from the blood; pure culture of the bacillus only from the blood of the heart.' Both accounts agree that there was malaria, and that there were no typhoid intestinal lesions. The evidence on which the recognition of the typhoid bacillus is based is not given, but this case is given so much attention here not because of yellow fever (AGRAMONTE gives the opinions of six consultants, all of whom considered that the case was not yellow fever), but from the point of view of the pathogenic relation of the presence of *B. icteroides*, viz., was it merely an accidental contamination, or had it anything to do with the illness? It becomes of interest to call attention to the work of the following observers, and to remark that the bacilli of GWYN and CUSHING (*vide infra*) were extremely typhoid-like when examined by the writer, for which without care they might have been mistaken.

The more exact relationship of the *B. icteroides* was established by REED and CARROLL[4] who found that it belonged to the so-called hog-cholera or 'enteritidis'

1. Wasdin and Geddings, *Report of U.S. Marine Hospital Service*, 1899.
2. No. 7, Wasdin and Geddings, l.c., and Agramonte, v. infra.
3. Agramonte, Reprints from the *Medical News*, February 10-17, 1900.
4. Reed and Carroll, *Medical News*, September 9, 1898

group of bacilli. It is from this point of view that the *B. icteroides* obtains greater interest, for there is a certain amount of evidence that members of this group are capable of giving rise to disease in man apart from yellow fever (*vide* references to several papers concerning 'food poisoning' given in the *British Medical Journal*, vol. ii, 1899).

More especially interesting are the outbreaks of so-called psittacosis, apparently due to the importation of parrots from South America (Buenos Ayres). And the cases related by GWYN[1] of a case of typhoid-like disease, presumably caused by a bacillus associated to this group; and by CUSHING[2] who made a very careful study of the relationships of his bacillus.

To return to AGRAMONTE's account, by using the same mode of taking blood as that used by WASDIN and GEDDINGS, namely, from the tip of the ear, although not unnaturally contaminations were met with, the *B. icteroides* was never met with; this, perhaps, hardly harmonizes with the supposition that WASDIN and GEDDINGS had derived their 'success' from bacteria washed from the skin. Thirty-seven cases were thus investigated. Blood was then taken directly from vein and planted in twelve cases into broth, in seven cases into milk, and in thirty cases upon agar; only in four cases did growth occur, and in none did *B. icteroides* appear. So that the findings were entirely negative both with peripheral capillary and systemic venous blood.

AGRAMONTE gives also the result of twenty-three autopsies performed upon yellow fever cadavers; in seven of these *B. icteroides* was met with (*i.e.*, 30·43 per cent.), at the same time much contamination or invasion was present, for out of the twenty-three not one appears to have been sterile; since forms of *B. coli* and cocci were encountered. Thus *B. coli* occurred 'constantly' in the liver and was also found in kidney, spleen, etc. Bacillus 'X' of STERNBERG and *B. pyocyaneus*, were also met with. It would not be profitable to discuss the reason of this very high proportion of contamination. Furthermore, three cases which were not yellow fever (including the above-mentioned case of P. Smith) also one of stabbing and one of combined ague, rheumatism and dysentery) yielded *B. icteroides* on cultivation. Next the serum of yellow fever patients (thirty-eight) was tried for agglutinative reaction in dilutions of 1:10 without positive result.

The serum of convalescents was also tried to see whether it would protect animals against injections of *B. icteroides*. So far as the experiments go they failed to shew a protective influence; the exact method of experiment is not detailed nor is the approximate multiple of the *minimal* fatal dose of the culture given, so that the value of the trial cannot be exactly appreciated. Lastly, the effect of the serum of convalescents was tried on four cases of yellow fever; one in which the treatment only began on the fifth day of illness died, the others recovered, but the account does not

1. Gwyn, Bulletin of the Johns Hopkins Hospital, 1898, IX, p. 54
2. Cushing, *ibid*, 1900, XI, p. 156

conclusively shew that the course of the disease was essentially modified by the injections, although the scheme is by no means without hope.[1]

The nett result of AGRAMONTE's work is that *B. icteroides* has nothing to do with yellow fever, and presumably appeared solely as a contamination. The relationship of the *B. icteroides* with yellow fever has been carefully questioned by the American Commission (REED, CARROLL, LAZEAR, and AGRAMONTE[2]); at first is recorded the examination of blood of eighteen patients withdrawn on different days of the fever (first to ninth) by means of a syringe from a vein at the elbow; the blood was put, in quantities of ½ c.c. into 10 c.c. broth. As a rule these blood cultures were sterile of all growth, in none did *B. icteroides* appear.

Further, eleven autopsies were made on yellow fever cadavers; in all of these SANARELLI's bacillus failed to appear in the cultures. No information concerning other organisms occurring in the cultures is given.

Next, in four cases blood was transferred from yellow fever patients to non-immunes; at the same time cultures were made in broth, three of these remained sterile, the fourth yielding staphylococci. Since in each of these cases yellow fever resulted as a consequence of the inoculation of the same blood into man, the authors argue that the exclusion of SANARELLI's bacillus as the cause of the fever is conclusively determined; the only apparent sources of fallacy in this conclusion would be (1) that the bacillus was so scanty that it happened to be solely in the samples injected; this, I think, may be fairly discounted; (2) that the broth used was insufficiently favourable for the growth of the bacillus; and (3) that the bactericidial power of the blood before transference to broth or of the resulting mixture of blood and broth was sufficiently high to kill, or to inhibit the growth of, the bacillus; the recognition of this last factor has been used in the cultivation of typhoid bacilli from living patients; but it probably has no effect upon cultivations made from organs to autopsies.

In summary in the three communications[3] these authors consider that the bacillus of SANARELLI can be definitely excluded from the etiology of yellow fever.

Our own observations at Parà are in accordance with this conclusion, as will be seen. The inoculation upon culture media of blood taken directly from veins (second, sixth, and seventh day) of different patients during life was only carried out on three occasions; in each case the broth used remained sterile (aerobic and anaerobic); cultures from blood from the ear-lobe were only made on two occasions; one of these yielded diplococci and tetrads aerobically, the other remained sterile. It did not seem to be a very profitable mode of research in the light of AGRAMONTE's experience.[4]

1. Finlay (Elstein and Schwalbe, Handbuch d. practl. med.) commenced this as a mode of prophylactic and therapeutic treatment in 1893.

2. Reed, Carroll, Lazear, and Agramonte, preliminary note, *Philadelphia Medical Journal*, October 27, 1900.

3. Preliminary note, *Philadelphia Medical News*, October 27, 1900, additional note, *Journal American Medical Association*, February 16, 1901, and experimental yellow fever, *American Medical*, July 6, 1901.

4. A number of flasks containing large quantities of broth were got ready, but owing to other observations they were left for a short time, and consequently became full of moulds and unusable.

At autopsy the technique adopted was to burn the surface of the organ thoroughly with the thermocautery over an area about 2-3 inches in diameter, the central part being more thoroughly charred; a large loop of 2·5 mm. platinum wire (13 × 3 mm.) was employed to convey material; three of these loopfuls was put into each tube. For fluids, such as pericardial and bile, drawn-out glass tubes were thrust through the wall after free cauterization; cerebrospinal fluid was taken in syringe by lumbar puncture after cleansing the skin with lysol solution. The liver, heart, etc., were always left *in situ* until the cultures had been laid; the spleen and kidneys were removed first (though in general I prefer to inoculate from the former before removal), Mesenteric glands, etc., were cut out with the thermocautery and held in sterilized forceps.

The primary inoculations were made into broth and dextrose broth and kept at 37° and at room temperature, *i.e.*, about 25° C.; later in some cases glycerine (5 %) broth was used. Both aerobic and anerobic (hydrogen and alkaline pyrogallol) conditions were used in each case. Whenever growth occurred and was found to be suggestive of typhoid-like or colon-like bacteria, the organisms were isolated and tried on fermentation tests with dextrose, lactose, and sucrose added to litmus-sugar-free broth.

An inspection of the tabulated statement on page 17, shews that in general our media remained sterile; altogether, cultivations were tried from thirteen corpses. If we may except the instances of the lymphatic glands, where the technique is more difficult to ensure freedom from chance contamination, it will be seen that coliform bacilli were only met with twice, when those from the different organs gave the same fermentative reactions and were presumably identical (all three sugars attacked in both cases). Another case yielded signs of general coccal infection (No. 6).

Only in one case (No. 2) was a member of the 'enteritidis or hog-cholera group' met with, and then only in the bile, but in pure culture. It was very actively motile and typhoid like; it did not grow luxuriantly like many other members of the group, and herein also was typhoid-like; it fermented dextrose, but not either of the other two sugars; in litmus milk whey it grew very poorly and remained faintly acid and almost clear, alkali formation only occurred after more than three weeks; parallel cultures of *B. icteroides* in whey began to go alkaline after about a week, whilst a culture labelled 'le sage' (kindly given by Surgeon-General WYMAN in Washington) went alkaline at the fourth day after the habit of the rapidly-growing GÄRTNER type of *B. enteritidis*. It appeared that this bacillus from *post-mortem* No. 2 was rather of the type of GWYN's and of CUSHING's[1] bacilli. The serum of two convalescents had no agglutinating effect upon this bacillus 'bile' at *post-mortem* No. 2 at 1 in 20 dilution. It would seem to be legitimate to argue that if SANARELLI's bacillus were of real importance in the etiology of yellow fever, we should have met with it in more than one single isolated instance, in which it will be noted that the liver, spleen,

1. Gwyn and Cushing, *Journal of Experimental Medicine*, 1901.

kidney, heart blood, and cerebrospinal fluid all remained negative. One other point, which may be remarked upon is the comparative freedom of bacterial growth in our series of autopsies, when compared to the records of SANARELLI, AGRAMONTE, and others. This may be partly due to the shortness of the period which was usually allowed to elapse between death and autopsy, to the care in thoroughly cauterising, and perhaps to the use of a spirit bunsen burner instead of the ordinary spirit lamp for heating the platinum wire and glass tubes. The broth we used showed itself very favourable for the growth of various bacteria when growth did occur or when plantings were made from other cultures. One mode of origin of the so-called agonal and *ante-mortem* invasion of bacteria which suggested itself, was the introduction of material by hypodermic medication which is often resorted to during the later and the agonal phases of the fever.

B. MOSQUITO TRANSFERENCE

It is incontestible that Dr. CHARLES FINLAY, of Habana, was the first to undertake direct experiments to substantiate his ideas of the part played by the mosquito in the transmission of yellow fever. His method was to feed mosquitoes upon yellow fever patients (not later than the sixth day), and then after an interval of from forty-eight hours to four or five days to allow them to feed upon susceptible persons ; the view was to produce a slight attack of the fever in order to produce immunity. At a delightful chat we had with the courteous doctor, on July 25, 1900, he told us many details concerning his experiments, which were commenced so long ago as 1881. Altogether, one hundred and two persons had been tried in this manner, and in seventeen instances some pathogenic effect had followed the bite ; this consisted in slight fever appearing about the fifth, sometimes as late as the fourteenth day. In no instance was there a definite attack of yellow fever as the result, but Dr. FINLAY thought that a certain immunity had been conferred since only four of these persons died of yellow fever, though the cases were followed out to ascertain their after history, in some cases for four years. Naturally it was not possible to exclude intercurrent infections by thus working in an endemic centre, still the mode and kind of experiment which has since led to more definite results was laid down. The kind of mosquito used by Dr. FINLAY was the *Stegomyia fasciatus* (it was referred to in his papers as *Culex* mosquito), he selected this kind on account of its town dwelling habits.*

* It may be noted that Dr. Reed's commission not only performed their experiments with his species, but were also indebted to Dr. Finlay for the eggs of the same (*Philadelphia Medical News*, October 27, 1900). The few cases tried with such short gnat incubation, as Finlay used, all turned out negative (*i.e.*, six in number) where the gnat incubation was less than ten days, in four of which, however, the gnat had been fed on the fifth day of illness of the yellow fever patient ; *i.e.*, near Finlay's six day limit. A seventh case surpassed this, as the gnat had been fed on the seventh day. These numbers may be compared with those of the negative experiments with longer incubations (v. infra.). There is, however, a source whence may have come the relatively few febrile reactions which Dr. Finlay obtained in his cases for he states (*Handbuch d. prakt med.*, Ebstein and Schwalbe art., Gelbes Fieber) 'one obtains a female mosquito from a house which is free from yellow fever infection.' In an endemic centre like Habana, it does not follow that an insect taken in a house of this description is necessarily uninfected ; so that it is possible that there were some accidental infections amongst such cases, though it may be more probable that independent accidental infection in the city should have taken place since there was no isolation ; still such difficulties were well insurmountable for a private individual, and credit should be afforded for a very astute presage of future experiment.

With great boldness, and fortunately without fatal accidents, Major REED and his comrades carried out a number of experimental inoculations of yellow fever in human subjects. These are reported in three communications, which, for reference, may be styled I, II, and III respectively.[1] The first two apparently successful inoculations were most unhappily somewhat vitiated by the accidental infection of Dr. LAZEAR, which, sad to repeat, was followed by fatal result, whilst engaged in more or less similar work to case 10 (I); this case, therefore, did not seem necessarily to be in consequence of the effect of the artificial inoculation.

In the succeeding cases efforts were made to keep the subjects away from the possibility of accidental infection. This may be summed up under three headings—(1) the presence of controls, (2) quarantining the subjects, and (3) locating the subjects outside the endemic area. The validity of the cases then depends upon the absence of spontaneous or sporadic cases amongst the controls, upon the efficiency of the supervision used upon those in quarantine, and the certainty that accidental infection might not occur from unguarded sources. It is perhaps to be regretted that more detailed account of the attempts to exclude accidental contamination were not given, especially the supervision at night. Again, the question of the isolation of the experimental camp leaves something to be desired, for instance, it is stated (II) that the camp 'Lazear' was 'about one mile from the town of Quemados, Cuba.' Quemados, it may be noted, is a straggling town, one street of which extends almost to the 'Quemados entrance' to 'Columbia camp,' in the grounds of which the experimental station, camp 'Lazear,' was situate; the railway line leading on to Marianao intervening between the two. Since the houses in this street were severely infected just previously to the commencement of the experiments, and that one next but one to the railway had been destroyed in consequence, for the judgment of the completeness of the isolation the distance from this region would have been useful. Again, the prevalence of yellow fever in the surroundings, and the possibility of introduction therefrom should be considered, as some distance further along the line a fatal case is reported from Marianao (v. Major GORGAS, November, 1900, Rep.). During the latter months of 1900 the fever seems to have been more prevalent in Habana than in the two previous years, *e.g.*, October, 1897, forty-two deaths; 1898, twenty-six deaths; 1899, twenty-five deaths; in 1900, seventy-four deaths. In November, 1900, fifty-eight deaths occurred, including cases from surrounding townships.

1. I, *Philadelphia Medical Journal*, October 27, 1900; II, *Journal of the American Medical Association*, February 16, 1901; and III, *American Medicine*, July 6, 1901.

The following gives a compact view of the successful cases :—The first column of numbers gives the reference numbers in Table I, p. 20, III ; the second, the identifications of cross reference to the cases as numbered in the separate communications :-

Number	Reference case	Incubation period. days	Day of fever on which gnat was fed	Number of gnats	Incubation in gnat. days	Total gnats	Total bites	Presumably infecting bites
1	10 (I)	3 dys 7 hrs	2, 1, 2, 4	1	12, 6, 4, 2	1	1	1
2	11 (I)	6 dys 2½ hrs	2, 1, 2, 2, 2	1	16, 10, 8, 1			
			2, 2, 2	1	12, 4, 10			
			2, 1, 1, 2, 2	1	12, 2, 4, 6, 10			
			1, 1, 1, 2	1	2, 4, 8, 6	4	4	3
3	1 (II)	3 dys 9½ hrs	2	1	15			
			2	1	15			
			2	1	19			
			3	1	21			
			3	1	21	5	5	5
4	3 (II)	5 dys 17 hrs	3	1	17			
			3	1	18			
			2	1	22			
			3	1	24	4*	4	4
5	4 (II)	3 dys 11½ hrs	2	1	19	1	1	1
6	5 (II)	3 dys 19½ hrs	3	1	20			
			3	1	21			
			2	1	25			
			3	1	27	4*	4	4
7	7 (II)	3 dys 23 hrs	2	1	24			
			1	3	12			
			1	4	8			
			1	7	5	?	?	
8	6 (II)	3 dys 22½ hrs	1	4	17	4	4	4
11	5 (III)	3 dys 23½ hrs	3	3	39	3	3	3
14	6 (III)	3 dys 2½ hrs	3	2	51	2	2	2
15	7 (III)	3 dys 6 hrs	3	2	57	2	2	2
16	8 (III)	2 dys 22 hrs	2	3	16	3	3	3

Whilst in the main the incubatory phase was so constant that the illness began during the course of the fourth day, there are two examples of considerable excess, viz., Nos. 2 and 4; in both of which the number of presumably infecting gnats was three and four respectively; thereby contrasting with cases 1 and 5, in which but a single gnat conferred the infection. Without laying too much stress upon variations of this character especially, because the experiments are naturally few in number, it is perhaps not unfair to remark that their validity depends upon the constancy of the watch kept upon the individuals after inoculation, and in the case of No. 16 during the latter part of the quarantine period.

Another point of interest is the comparative mildness of the illness produced and the absence of fatal result.* It may be noted that the naturally acquired and fatal attack, which unfortunately carried off poor LAZEAR, was ascribed to the bite of a single mosquito. In personal conversation with Major REED I gather that he attributes these results to the early stage at which the illness was recognized and treated by rest. Another point in regard to the naturally acquired fever is that in many, if not in most cases, exposure to infection leads up to, if not after, the time the patient is taken ill.

Major REED and his colleagues further showed that the blood of yellow fever patients, at any rate at the early stage, is capable of conferring the illness by the direct transference of blood from sick to healthy; thus 2 c.c. taken early on the second day, 1½ c.c. taken twelve hours after commencement of fever, ½ c.c. taken on the second day, and 1 c.c. taken twenty-seven and a half hours after commencement of fever all caused attacks of the fever.

In these papers the authors compare the nature of the fever to that of malaria partly because of the incubatory period of ten days or more necessary in the gnat; this, indeed, would be equally essential for a gnat inoculation of bacterial parasites, provided that the inoculation were not simply due to contaminated biting parts, which can certainly be discounted from the experiments of FINLAY in so far as he was never able to reproduce typical yellow fever in his cases. It is only natural to suppose that a bacterium must also be allowed the time element in order to multiply sufficiently to be able to give an infecting dose whether the organism passes directly or indirectly into the ejecting apparatus of the gnat. Again the direct transference of blood from patient to experimental individual was tried because (II) 'It seemed to us that yellow fever, like the several types of malarial fever, might be induced by the injection of blood taken from the general circulation of a patient suffering with this disease.' This, though undoubtedly true of the animal parasite of malaria, is also possible in the case of bacterial parasites, as is a common laboratory experience when direct inoculations are made from one animal to another.

In experiments with the transference of bacterial parasites by means of biting

* More recently, according to the daily press, some fatal results have occurred: details as yet are wanting.

insects the time factor does not seem to have been considered. Thus NUTTALL[1] shews that bugs and fleas which had been fed on animals full of plague and other bacteria were incapable of giving the disease to other animals when directly transferred to them ; whether they could have done so after an incubation period, and whether the bacteria could have been discovered in their salivary or ejecting apparatus is not known.

Another point which also reflects upon the mildness of the fever conferred is the small quantity of albumin in many in the urine in the experimental cases ; thus out of the twelve gnat infections in five the quantity is described as a 'trace,' and in one other there was no albumin until thirty-six hours after the fever had subsided.

The control cases were formed by the seven susceptible persons accommodated at the experimental station camp 'Lazear' (II), where the incidence of the fever 'was strictly limited to those individuals who had been bitten by contaminated mosquitoes.' It may then be taken as proved that *Stegomyia fasciata* (*Culex*) may be capable of conferring the disease some ten, twelve, or more days after having fed upon yellow fever patients during the first, second, or third day of the fever. The cases which were bitten by gnats which had been fed upon yellow fever cases later in the disease, viz. :—

Case 6 (I) one mosquito fed ten days before on fifth day of fever,

Case 8 (I) one mosquito fed thirteen days before on fifth day of fever,

Case (III, p. 18) one mosquito fed forty days before on fourth day of fever,

proved negative. The question of how long the infective agent remains in the circulating blood, whence it can be extracted and transferred by gnats is important for combatting the prevalence of the disease by means of isolation. It can hardly be doubted that the infective agent does not remain for prolonged periods in the circulation of those who have passed through the disease, otherwise it is difficult to understand the comparative readiness with which the disease disappears in localities, or has done so in the past, without any overt act directed against the gnats. Conversely there is a tenacity with which the fever remains endemic in the Latin-American countries of Central and South America ; here there are four possibilities : one already dealt with, the continuance of the parasite in the circulation of the 'immune' ; second, the occurrence of second or further attacks amongst the 'immune,' with which may be included more or less primary attacks in the children of the 'immune' ; thirdly, the prolonged survival of infected gnats ; fourthly, that the infecting agent is able to remain alive independently of man and gnat.

Apparently it is with the third method that Dr. REED considers that the foci of the fever are maintained by proving that two gnats *(S. fasciata)* which had been kept for fifty-seven days after their infecting feed upon a yellow fever patient on the second day of illness, were capable of conveying the infection to a susceptible person

1. Nuttall, *Zur Aufklärung der Rolle, welche Insekten bei der Verbreitung der Pest spielen u. s. w. Centralblatt f. Bacteriologie*, I Abth XXII, 1897, p. 87, and *Zur Aufklarung der Rolle welche stechende Insekten bei der Verbreitung von Infectionskrankheiten spielen*, ibid XXIII, p. 625.

(Case 7, III). If this should prove to be the sole mode of persistence of the contagium, the suggested analogy with malaria ceases so far as we yet know the natural history of the latter complaint, it is rather the persistence of the parasitic agent in the human host, which is chiefly responsible for the endemicity of the disease, and in Texas fever also this seems to be the case.[1] Although in yellow fever the contagium may not persist in the circulation, its temporary occurrence in the blood of natives and their children may be an important factor. From this point of view the occurrence of second attacks or of attacks amongst the natives is of considerable importance, or, to put it more precisely, the occurrence of attacks of fever amongst these people, which, though due to the yellow fever parasite, does not manifest diagnostic symptoms of the fever, which is only to be expected in the presence of a comparative degree of specific immunity.

The following is an instance of an early second attack or remote relapse with fatal ending :—A.P.D.S., thirty-three years, taken ill thirty days after arrival at Parà; when seen on the eight day he was much jaundiced and had a high degree of albuminuria; there was vomiting but no fever; the icterus and albuminuria gradually diminished, and ten days later he was discharged from the hospital. Six weeks after this he was readmitted with two days illness; he had fever and slow pulse (T. 39°, P. 70), much albuminuria; uraemia had already set in, and with constant hiccough he died on the fourth day of the new attack; unfortunately no *post-mortem* examination could be obtained. In both instances the diagnosis of yellow fever seemed indicated. Two or three persons whom I have seen have told me that about a month or so after they had yellow fever they had a sort of relapse of attack, and it is possible that the monthly recurrence of 'malaria,' which is talked of in Parà, is of an allied nature. For quarantine purposes, I am disposed to think that a period of six or seven weeks should have elapsed since an attack of yellow fever before an individual should be classed as an 'immune.'

Again, it reads rather more satisfactorily that a man (Case 3, II) was nine days in quarantine, than that another was (Case 7, III) seventy-eight days, which appears rather a long time for certain knowledge of all his movements short of absolute incarceration. Still, apart from these criticisms, the striking feature of the experiments is the statement that amongst the local community *only those persons who had been subjected to artificial inoculation contracted the disease.*

The first nine experiments (I) were uniformly negative: of these an eight-day period in the gnat was the maximum, except in two cases, where it was ten and thirteen respectively, but the sources were very mild cases on the fifth day of disease. In the latter cases it is shewn that not every gnat which has been fed upon a yellow fever case during the first three days of illness is capable of conferring the fever.

1. Theo. Smith, *The Aetiology of Texas Cattle Fever. New York Medical Journal*, July 8, 1899.

NEGATIVE CASES

Number	Species of gnat	Date of fever of source	Days of incubation in gnat	Total gnat bites
1 (II)	*S. fasciata*	5th day, severe	11 & 14	
	S. fasciata	3rd day, severe	6 & 9	2
2 (II)	*S. fasciata*	3rd day, moderate	12*	
		2nd day, well marked	10†	
		3rd day	15*	
		2nd day	13†	4
4 (II)	*S. fasciata*	2nd day, severe	10*	
		2nd day	13*	
		2nd day	17*	
		3rd day, fatal	12	4
5 (II)	*S. fasciata*	3rd day, well marked	12*	
		3rd day	15*	
		3rd day, well marked	18	
		3rd day, well marked	18	4
ix (III, p. 18)	*S. fasciata*	1 day	22	12
xx (III)	*C. fungens*	?	19	5

Leaving the last two out of account, and taking the twelve successful inoculations, this gives a proportion of failure in 25 per cent. From this we may take it that there is not always a sufficient number of the parasitic agents in the blood of a patient on the second or third days to infect a gnat, so that it becomes able to pass it on when feeding on a susceptible person. This suggests the conclusion that the parasite would not be discoverable in an ordinary pair of coverglass films, supposing that one, or quite a few, are sufficient to cause infection of the gnat, for the amount of blood, etc., taken by the gnat is greater than that used for such films. Hence, perhaps, the examination of plain blood films has been hitherto without avail.

The commencement of an attack of yellow fever and the time of infection has often been said to be during the night. In view of this the report of Major REED (III, p. 21) says 'If the hour of inoculation in all of our cases should have taken place at about sunset, then with the same period of incubation, seven, or 43 per cent., would

have experienced their attacks at night.' By reducing the times of inoculation of these sixteen cases to noon and midnight and 6 o'clock morning and evening, and also considering the hours about 6 o'clock as neutral we find that if the inoculation had been at :—

6 a.m.	the onset would have been	during	the night	in ten cases.
Noon	,,	,,	,,	,, three cases.
6 p.m.	,,	,,	,,	,, five cases.
Midnight	,,	,,	,,	,, twelve cases.

So far as this mode of argument is feasible it shews that the greatest number of onsets during the night would have been from night biting mosquitoes, infecting at midnight; in Parà this is incompatible with *S. fasciata*, but compatible with night mosquitoes as *C. fatigans*. The next largest figure is that for 6 a.m. infections, this is compatible with the bites of *S. fasciata*.

Whilst it would not be profitable to enter into all the occupations in their liability to yellow fever danger, we were much struck by the number of bakers that we saw as yellow fever patients, thus out of five hundred and twenty-nine cases as many as thirty were in bakers; the nature of their trade was suggestive of much exposure to mosquito bites.

As an indication of the position of the belief that the fever is usually caught at night, the following quotation from DE AZAVEDO SODRE and COUTO may be made :— 'As soon as an epidemic of yellow fever commences, many foreigners and unacclimatized persons as well as all well-to-do families, withdraw from Rio de Janeiro and Santos to Petropolis and Sao Paulo respectively, thence they travel daily by early trains to the city, and return again in the evening. Now, although they remain in the pest-laden city from 10 a.m. to 4 p.m., and eat and drink there without any precautions, they escape infection in all epidemics. Those, however, who for one reason or another have to remain overnight or for several nights in the city are often struck by the fever. This circumstance shews the necessity of avoiding spending the night in places which are infected with yellow fever.'[1]

The incubation period in gnat-infected cases (III) gave an average of nearly four days with the twelve cases (three days twenty-two hours), but the last case is of interest in having so short a period as two days twenty-two hours (provided that there was no previous accidental contamination). Compared with malaria this is extremely short, for in experimental cases a much longer incubation period has been established: Tertian, sixteen to twenty-five days; Aestivoautumnal, twelve to sixteen days.[2]

In tsetse disease in rabbits, the first rise in temperature is generally about the eighth or ninth day; certainly small animals (rats) will die as early as the sixth day

1. *Nothnagel*, vol. IV, p. 302.
2. Fearnside, *Sci. mem. of med. officers of Indian army*, XII, 1901.

after infection, but then the number of parasites introduced is relatively far larger than would be the case probably in gnat-borne yellow fever.

In Texas fever[1] the incubation between injection of blood of sick animals and onset of fever 'may be in from six to ten days, depending upon the number of microparasites originally introduced, the predisposition and age of the animals, and the season of the year.' With inoculations by means of young ticks 'the high temperature appeared generally in fifteen days after the first young ticks had been put on the animal.

Another point in comparing yellow fever with a zooparasitical disease like malaria is the question of the fertilization of the gnats; it seems to be that the proper sexual conception of the female *Anopheles* is essential for the development of the malarial parasite; the report of the U.S. Commission is silent upon whether the successfully-infected mosquitoes were fertilized or brought forth eggs. Whilst there may be no direct connexion of the fertility of the transferring insect, with its capability of fostering an animal parasite, possibly the mere increased nutritional circumstances after a feed of blood would be sufficient for aiding the development of bacterial parasites.

Another point in which yellow fever differs from the known infections caused by protozoal parasites is the absence of splenic enlargement, which is found in malaria, Texas fever, and tsetse fly disease. Though certainly, it must be admitted, that our knowledge of diseases of this nature is too scanty for discussion.

The points then which seem at variance with a zooparasite in yellow fever are (1) the shortness of the natural incubation period, (2) the readiness and rapidity with which the parasite disappears from the blood, (3) the considerable degree of immunity[2] which is rapidly attained, (4) the short course of the illness and the usual absence of remote relapses or recurrences, and (5) the absence of splenic enlargement. At the same time none of these are incompatible with diseases of bacterial origin.

In regard to the uncertainty of diagnosis in some cases and their importance in the continuance of the disease, the following remarks may be made:—In Cuba a special form of fever, which is termed 'Borras' (or Fiebre de Borras), is recognized amongst the inhabitants (generally juvenile); this has been considered distinct from yellow fever by Cuban physicians. In Parà the fevers of children seem usually diagnosed as 'Febre palustre'; throughout Brazil another fever called 'Febre remittente bilioso dos paizos quentes' (remittent bilious fever of hot countries).

1. Smith and Kilborne, *Investigations into Texas or Southern Cattle Fever*, Washington, 1893. pp. 15 and 106.

2. Theobald Smith and Kilborne, p. 134; 'These experiments demonstrate the important fact that one attack of Texas fever does not necessarily protect the animal from a second attack. Of the eighteen cases seven may be said to have remained practically unaffected during the second exposure. Of the remaining eleven three died during the second exposure. . . . . Hence we must be careful in giving even in these cases too much credit to the first attack in warding off the second following one. . . . . But it may be laid down that as a general proposition that a single attack is not sufficient to produce complete immunity.'

'Borras' fever[1] 'is a pyrexia most frequently attacking children, though it may occur at other ages. It is characterized by vomiting—abundant or scanty—lasting a few hours; or the days of the febrile attack rarely pass without this disturbance; occasionally there is albuminuria but never gastric haemorrhage, epistaxis, melaena, petechiae, hiccough, or icterus. It may occur more than once in a lifetime; both whites and coloured are attacked—most frequently whites up to the age of twelve to fourteen years; the mortality may be as high as 30 per cent.' On the other hand, JUAN B. FUENTES[2] says that haemorrhages occur and that when 'icterus and albuminuria are present it may be confounded with yellow fever or icterus gravis.' So that there is some degree of uncertainty as to what borras fever is. Anyhow, it is regarded with great suspicion as being merely one of the many clinical types of yellow fever; thus in the report of vital statistics of Habana, etc., for July, 1901, by Major GORGAS, we find :—'We make the best record ever made before for July, having had only four cases and one death. Two of these cases (both of which were reported as 'Borras' and one of which died) occurred in children of Cuban parentage, born in Habana, having lived in this city continuously since birth. The physicians of Habana, as a body, do not recognize this disease as being yellow fever, and indeed, both in its symptomatology and pathology, it differs widely from the disease in the adult; but the board, to which all cases of yellow fever are referred, after careful consideration, and in one of the cases after a careful autopsy and histological examination of the organs, concluded that the two cases were yellow fever.'

In Parà it was seemingly impossible to get people to appreciate the importance of the complete diagnosis of malarial fevers by the microscope, and the impossibility of doing so in patients filled up with quinine; consequently we were rarely able to decide in mild cases of transient fever which passed as 'febre palustre.'

In one cottage I came across a family in which two children had recently died, and a third was moribund; the nearest known *Anopheles* breeding place was fully half-a-mile away and separated by trees; the parents were unaffected. Unfortunately it was not possible to make any proper examination, and an autopsy was out of the question; still it seemed clear that some intense infection was present. There was no rash or icterus there, the condition of the child seemed almost meningitic. Vomiting seemed to have been the chief symptom, besides 'fever.'

With regard to the 'bilious fever' none of the few cases which I saw diagnosed as such, agreed with the symptoms laid down by TORRES HOMEM[3]; they were all in recently arrived individuals, and there did not appear any definite reason why they should not be classed as yellow fever. In TORRES HOMEM's account we find that this bilious fever or 'febre amarelle dos acclimitados' is very common in Rio, especially during the summer (*i.e.*, the yellow fever period), and that it is the dwellers

1. *Luis Perna y Salomo, Revista medicina tropical Habana*, Tom II, p. 49.
2. Juan B. Fuentes, *ibid*, Tom I, p. 75.
3. Torres Homen, *Estudo clinico sobre as febres do Rio de Janeiro*, 1877.

in the city that are chiefly attacked; whilst in the great foci of paludism outside the city, and especially outside the municipal limit, *febre remittente biliosa* is very rare. In giving points for differential diagnosis from yellow fever, he says that 'the presence of an epidemic of yellow fever should always form a point for differential diagnosis'; supposing that the relationship to yellow fever is more essential, the disregard of such cases would be just apt to foster the yellow fever and to ensure its reappearance.

GUITERAS[1] makes the following significant statement: 'The bilious remittent fever, that in our old text-books of medicine occupied so conspicuous a place in tables of differential diagnosis with yellow fever, has practically disappeared from the Southern Sea border since yellow fever ceased to be endemic there.' It is clear that in endeavouring to rid a neighbourhood of the yellow pest, notice and suspicion must be cast upon cases in which this other diagnosis is made, and they must be dealt with accordingly. DOMINGOS FREIRE isolated a colon-like bacillus as the cause of the bilious fever, but said nothing concerning the malarial parasite; which, however, may occur in mixed yellow fever and malaria. On the other hand, AZEVEDO and COUTO look upon this bilious fever as a clinical form of malarial ('haemoglobinuric palustral') fever with icterus. It remains to be seen whether the condition is due to some further implantation in an old malarial patient of other organisms than that of malaria; naturally the mere presence of the malarial parasites will not exclude the possibility of other factors.

It is generally stated that second attacks of yellow fever are rare, and that therefore the immunity against the disease is very complete. However, it is also commonly accepted that this immunity breaks down if the individual is long absent from infected regions, so that in reality it would appear that the acquired immunity is of comparatively short (say a few years) duration; constant exposure or rather constant reinfection is therefore essential for continuance of immunity. It is not to be expected that a typical attack will occur in a partially immune individual unless he has received a very severe dose of the infective agent.

The following example is one of a not very typical attack occurring in an individual who had had yellow fever twelve years before at Pernambuco, and who had been engaged since in and about Brazil. Taken ill suddenly in the afternoon with rigor, temperature 101°, pulse 80, and took large dose of quinine. There was no typical facies; some headache, much bilious vomiting, which continued for three days; on the third day there was a trace of albumin in the urine, which soon cleared up. Temperature and pulse:—

2nd day—morning temp., 102·6°, p. 86; afternoon temp., 102·6°, p. 88;
3rd day—morning temp., 103·6°, p. 90; afternoon temp., 103·8°, p. 90;
4th day—morning temp., 99·2°; afternoon temp., 99·4°;

after which the temperature became normal. There was no icterus. Malaria parasites were not looked for on account of the quinine, but there did not seem any reason from the clinical side to suspect malaria.

1. Guiteras, *Report of U.S. Marine Hospital Service*, 1898, p. 299.

V. OWN OBSERVATIONS ON YELLOW FEVER ETIOLOGY

On the accompanying table will be found the results of our examinations of the *post-mortem* material.

The course of our investigation was chiefly directed at first to the search for some protozoal parasite, but it so happened that, especially in the specimens of the mesenteric glands out of the first autopsy, we were much struck with the presence of a fine minute bacillus in some quantity. At the next autopsy, especially in the observation of the fresh spleen juice, we were so much struck with certain curious elongated structures of protoplasmic nature, that we spent much time in searching for these and other similar bodies in tissues of subsequent autopsies and in blood of living patients. Eventually we proved that these structures were artificial, by producing them from our own blood. About the same time we came to the conclusion that possibly the investigation of mosquitoes captured in suspected houses might give a lead for further work. Almost the first of these (a *C. fatigans*) dissected on 6th December, 1900, showed large numbers of what instantly reminded me of the bacillus we had encountered at the first autopsy, some others gave a like result. We then commenced to stain and examine the material prepared from the other autopsies for this organism particularly. Owing to the scanty numbers which were found in given specimens, this process of examining took some time, and the thorough search through the old material was not finished when we were taken ill ; meanwhile, material obtained at other autopsies was examined, and careful search again and again revealed its presence. Since there was a suspicion that possibly a bacillus found in such small numbers might be merely an accidental incomer, attention was paid to see where it could come in. The points at which contamination might occur were in the preparation of the film from the organ, this was excluded by care in searing and using recently-heated capillary tubes to obtain the juice ; the freshness of the cadaver at the *post-mortem* and the frequent sterility of the organs by culture showed that no gross contamination usually took place.

The possibility of the presence of organisms on the coverglasses from the water in which they had been washed led us only to employ ones which had been thoroughly heated by the spirit lamp on a piece of wire gauze nearly to redness just before use. Since the organisms clearly appeared in the film and not superposed to it we did not think it likely that it could have got in during the staining of the dried flamed film ; however, besides using the stain as heretofore with five per cent. carbolic acid in its constitution, we tried washing out also in carbolic, and only using recently sterilized Petri dishes for the stain and the washing. It was difficult to see what other

Number	Initials and Age		Remarks
I	P.V.		Albuminuria. Icterus. Anuria. Vomito negro in stomach. Fatty liver.
II	C.A.	= +	Vomito negro. Albumen. Icterus. Haematemesis. Stomatorrhagia. V. negro in stomach. Fatty liver.
III	Md. J.		Vomito negro. Albumen. Not icteric. Hiccough. Uraemic epileptiform convulsions. V. negro in stomach. Fatty liver. Spleen large, pigmented, malarial
IV	A.F.		Albuminuria. Black vomit. Yellow after death. V. negro in stomach and intestines. Fatty liver.
V	M.V.		Devoted to examination of organs in fresh state. Icterus. Albuminuria. Suppression. V. negro in stomach. Fatty liver.
VI	M.D.		Icteric. Enterorrhagia. Mania. Suppression. No black vomit in stomach. Liver very fatty.
VII	G.M.		Icterus. Albuminuria. Suppression. Fatty liver.
VIII	F.S.G.	= +	Icterus. Albuminuria. Suppression. V. negro in stomach. Very fatty liver.
IX	G.	= +	Albuminuria. Icterus. V. negro in stomach. Liver fatty.
X	M.B.	age = o	Very obese. Not yellow. Albuminuria. Stomatorrhagia. Suppression. Stomach no V. negro. Haemorrhage in lung. Very fatty liver. Atrophic cell changes.
XI	B.C.	= + = + = o = o = o	Icterus. Albuminuria. Stomach coated with V. negro. Fatty liver. Spleen large, pigmented, malarial.
XII	J.C.	= +	Icterus. Albuminuria. Black vomit. V. negro in stomach. Fatty liver.
XIII	D.S.		Icterus. Albuminuria. V. negro in stomach. Fatty liver.
XIV	M.L.	= + = +	Icterus. Albuminuria. Black vomit. Reddish-brown watery content in stomach. Black coating small intestine. Fatty liver.
XV	G.V.		Icterus of juices, *post-mortem*. Epistaxis. Enterorrhagia. Fatty liver. Much disintegration microscopically. Spleen large, dark, malarial.
XVI	F.E.	= + ht abundant +	Icterus. Albuminuria. V. negro in stomach. Very fatty liver.
XVII	V.Z.	= + ry abundant	Yellow, *post-mortem*. V. negro in stomach. Fatty liver. Spleen large, pigmented, malarial.

ling of small bacillus.

(Table to face p. 26).

precautions could be taken, yet still the fine small bacillus appeared. Later the plan was tried of putting a large number of big loopsful into saline solution with a small quantity of corrosive sublimate, and after several good shakings allowing the stuff to sediment; thereby it was hoped that possibly in the lower part of the tube one might be able to concentrate the bacilli from a larger quantity of tissue than could be examined otherwise. The method is merely an application of the common technique in examining doubtful sputa for tubercle bacilli. At the same time ordinary smears were made for control. In this way we found the small fine bacillus with greater facility than in the plain smears.

At the earlier stage when examining centrifugalized blood we had sometimes examined the bottom of the tubes for bacilli, but without much success; further examinations of early cases were to have been made by allowing slow sedimentation to occur whereby time would be allowed for the heavier particles to sink first, which is not the case when slightly diluted blood is centrifugalized in a narrow tube. The method was tried in rather long tubes with the borax-boracic acid mixture used for tubercle, but no early cases were obtainable at the hospital except a man from a ship nearly all of whose crew were affected with yellow fever, a disease which he had already had some years before; besides tertian parasites in his blood, the sediment yielded a small bacillus similar to that in the yellow fever cases; a control case of malaria examined at the same time with the same batch of tubes and medium gave negative result. It was certain that he had been exposed to yellow fever infection on the ship, and it was possible that these bacilli were the consequence, though the course of his temperature corresponded with the ague infection.

Naturally we turned to Dr. STERNBERG's book, to see whether this assiduous observer had recorded anything similar to the small bacillus which we found. The following may be quoted:[1] 'I have had my attention especially attracted by an extremely slender and long bacillus which has been very abundant in many of the smear preparations, but which has never shewn itself in my cultures (contents of alimentary canal). It is the smallest organism so far as its breadth is concerned that I have yet encountered; it is a flexible filament, as shewn by the various shapes it assumes, and may reach a length of fifty micromillimetres or more.' This turned our attention to the examination of the faeces, and, at our final autopsies, the intestinal contents, and we found an extremely fine bacillus, sometimes in extraordinary numbers, so that in a whole field of a $^1/_{12}$ O.E. objective there were but few other kinds of bacilli; we did not see such lengths as STERNBERG mentions; its tenuity was such that by opening the aperture of the condenser to a point at which the larger ordinary faecal bacilli were still visible, the fine one completely disappeared; in such examinations of fresh unstained faeces, no motility could be detected. Like the bacillus found in the tissues it did not stain with great readiness; thus, F.G., seventh day,

1. Sternberg, *Report on the etiology and prevention of Yellow Fever*, Washington, 1890, p. 113.

stool with mucous pieces; film stained for ten minutes in somewhat diluted carbol fuchsin, large numbers of 'small bacillus,' but unstained; staining prolonged overnight; 'small bacillus' now stained and present in large numbers. Besides faeces it was also seen in small numbers in a few specimens of black vomit; in one case (*post-mortem* 17) there were very large numbers in the duodenal contents; the ileum, as in other cases, showing vast numbers of coliform and other faecal bacteria. In the contents of the colon, also, the 'small bacillus' was met with in abundance. Whether from the nature of the balsam used or from the cloveoil, etc., which was put in the boxes to prevent destruction of the labels by insects, etc., the colour of all our mounted specimens faded out and diffused. Since my return I have tried to re-stain these specimens (prolonged carbol fuchsin and aniline gentian violet) but for some reason, apparently, the bacilli must have lost staining power; I have not succeeded in finding them in specimens which showed large numbers when they were first made. Further, it appeared suggestive that STERNBERG had met with an identical organism in tissues. Referring to the examination of sections of various organs, he says[1] 'The result of this research has again been negative, so far as the general presence of any particular micro-organism in the material examined is concerned. But in one case (No. IV) I found in the kidney a minute bacillus which apparently invaded by preference the glomeruli. It was not found in the capillaries generally, but a certain number of foci were found, some small, as shown in Fig. 6, and involving only a portion of the glomerulus, others involving a whole glomerulus, and the tissues immediately surrounding it. The appearance was such as one would expect to see in a case in which solitary bacilli, carried in the first case by the blood current, had effected a lodgment and established a centre of infection in tissues already, perhaps, necrotic and through which the circulation had ceased. The latter supposition seems to be justified by the fact that there were comparatively few of these foci, whereas if they had been established while the circulation was still going on, we would expect to find numerous secondary foci and a certain number of bacilli in the neighbouring vessels. Moreover, there was no evidence of inflammatory reaction as a result of this invasion of the tissues by parasitic organisms. I am, therefore, of the opinion that this is some ordinary saprophyte which had effected a lodgment in the kidney, possibly during the last hours of life when the vital resistance of the tissues was slight, or when as a result of the blood stasis in the organ local necrosis had already occurred at certain points before death.'[2] (It may be noted that this autopsy was performed one and a half hours after death; whether the interpretation given is the right one does not necessarily follow). 'It is quite probable that during the last hours of life a certain number of micro-organisms from the intestine succeed in passing through the enfeebled tissues into the interior of the capillaries and are carried away by

1. *Op cit.*, p. 138.

2. The condition described is, perhaps, in accordance with the distribution of an anaerobe.

the already slowly moving blood stream to distant organs, where they may establish centres of growth even before death occurs, or are at least in position to take possession of the field, as soon as the vital spark has been extinguished. In the case in question, I believe that the true explanation of the presence of the organisms described is that suggested, for I have not found in the other cases examined any similar collection of bacilli, and can, therefore, not attach any importance to the observation so far as the etiology of yellow fever is concerned. In Berlin I fell upon a little group of slender bacilli in a capillary of the liver, and recently have found a similar group in a preparation of skin from a yellow fever patient[1] . . . . The bacillus above described, present in a single case, is then the only micro-organism found in the material obtained in Havana in 1887, so far as liver and kidney were examined.' When in Parà we thought that possibly the discovery was due to accidental successful staining of the bacillus which we met with; since my return staining of sections (paraffin) of the material obtained has not been successful in revealing groups of bacilli as had been hoped; some suggestive appearances have been seen after heavy carbol fuchsin, aniline fuchsin and violet staining, but nothing definite enough for satisfactory recognition; it is possible that the xylol, etc., used for the embedding has caused the same change as has occurred in the faecal specimens.

In his conclusions[2] Dr. STERNBERG remarks: 'Some of the micro-organisms present in the dejecta of yellow fever patients, as shown by stained smear preparations, have not developed in the cultures made, either aerobic or anaerobic. One extremely slender filiform bacillus, which can only be seen with high powers, and which is quite abundant in some of my preparations, has never been obtained in the cultures made, and, no doubt, there are others of the same category.' . . . Attention may also be called to some of the photographs given by Dr. STERNBERG; whether the organisms represented are the same as the other small bacilli cannot be said; anyhow the sources of the cultures were not pure, and the investigators not very expert bacteriologists. On Plate XV, Fig. 6, is a figure of a fine bacillus found in a sample of DOMINGOS FREIRE's vaccine (which was supposed by that author to be a pure culture of his 'cryptococcus'); the specimen was stained with gentian violet and does not appear to have been coloured very intensely. On Plate III, Fig. 4, there also occurs a small bacillus concerning which he writes[3]: 'is from a slide mounted by Dr. ANGEL GAVINO YGLESIAS in Dr. CARMONA's laboratory. Associated with the large bacillus shown in the photograph, there is another slender bacillus in smaller number, which is seen on looking over the slide' (it also appears more faintly stained). Dr. STERNBERG does not appear to have thought of connecting these various fine bacilli with one another; it is not possible for us to identify them as one and the same organism, but the quotations are of some interest in connexion with our own observations.

1. *Loc. cit.*, p. 140. 2. *Loc. cit.*, p. 222. 3. *Loc. cit.*, p. 164.

With regard to cultivating the small fine bacillus, our attempts were practically a failure. We used to cut out several of the mesenteric glands by means of the thermocautery and introduce them into the broth tubes by means of recently-heated forceps. In two cases we got a growth (in one case pure and in another case with another bacillus) in this manner; the tubes were placed in hydrogen with pyrogallol and alkali. In the former case there was no apparent change in appearance, but on breaking up the gland large numbers of apparently growing 'small' bacillus was found. In another case a mixed culture of *Staphylococci* and the small bacillus was obtained; subcultures in these cases failed to give any growth of the small organism. It is, perhaps, noteworthy that in a large proportion of these whole mesenteric gland cultures no ordinary faecal, etc., bacteria grew, though from the large size of the pieces, it might have been anticipated, that accidental contamination would have occurred, or that SANARELLI's bacillus would have appeared. It appeared desirable to search for a medium which would be favourable for the growth of the organism, and the last thing done before being taken ill was to make several brews of tissue from the last autopsy and also to prepare milk tubes. Upon returning to work these were full of moulds and could not be utilised at the last two autopsies I was able to obtain. It seemed then that a peculiar small fine bacillus was to be found in the organs of yellow fever cases, in the contents of the gut, in local spots presumably gnat bites on the skin, and in the stomachs and salivary sac (or oesophageal diverticula) of many of the gnats examined. Piecing this altogether, it suggested that the fever consisted in a gnat-borne and introduced infection, and that the small bacillus was the active agent. It may be noted that FINLAY in his original mosquito theory looked to the inoculation of a bacterial parasite (a tetracoccus) by means of his mosquito.

As a means of seeing whether a recognizable bacillus could be traced in the mosquito, a number of preparations of the stomachs and salivary (or accessory) sacs were made from mosquitoes which were caught at the leprosy asylum at Parà inside the cottages of the lepers; some of these had obviously been feeding upon the serous subcutaneous exudation rather than actual blood. These specimens were made just before coming away, and were not stained for the leprosy bacilli; now, unfortunately, they have become mislaid. It may be added that by the notes made of the appearances in the fresh state of the organs of these mosquitoes they were all devoid of the small bacilli found in other places.

Soon after we had found the small bacilli in the brown night-biting gnat, *C. fatigans*, we received the first report of Major REED's Commission, in which the day-biting *S. fasciata* was incriminated; the proof then was slight, and we thought that possibly their successful cases were due to the accidental bite of a night mosquito like ours. That the *S. fasciata* can convey the disease has since been proved. It seemed probable that if a bacterial parasite was concerned, and that subcutaneous

introduction as by gnat bite was necessary for reproducing the fever in man, it might be that the bacillus could be swallowed by the mosquito from other sources than an actual bite on a yellow fever patient. A number of a pupae taken from a cesspool (species *C. fatigans*) were tried, but the results were not satisfactory from the external contamination and the extensive cytolysis proceeding in the creature. Another attempt made, was to catch mosquitoes coming directly up a large ventilating pipe from a sewer, but the whole thing was washed away by a rain shower. It seemed possible that a feed of blood might be requisite to supply pabulum for the growth or spread of the bacillus within the body of the gnat.

The implication of a sewage-loving gnat, like *C. fatigans*, and the fertile source of it in foul water and cesspools was thought possibly to be an explanation of the outbreak of cases of yellow fever in apparently isolated and spontaneous manner. Altogether about eighty mosquitoes were dissected; but all of these were not examined for the small bacillus; the method adopted was to remove the salivary sac and also the stomach by dissection under a lens; examine in the fresh state between two coverslips in saline solution, and then by drawing the glasses apart they were ready for making stained specimens. Out of thirty-five individuals of *C. fatigans*, small bacilli, sometimes in large numbers, occurred sixteen times; out of thirty individuals of *S. fasciata* it occurred only six times. These were insects caught in suspected houses and on a ship with yellow fever. Preparations were made for rearing insects from the egg in clean waters, so that when fed upon patients there would be no possibility of chance contamination. Although several attempts were made we never succeeded in getting the species *C. fatigans* beyond the young larval stage; with *S. fasciata* there was no difficulty, the first lot began to hatch out just as we were taken ill, and afterwards a new lot was started; when they were ready I was unable to get hold of an early case to feed them upon. So that no observations upon reared cleanly mosquitoes which had actually been fed on yellow fever cases were made.

As a working theory of the pathology of yellow fever, derived from these observations it was thought that:—

Supposing the 'small bacilli' found in the 'typical bites,' organs, salivary sacs, and stomachs of the mosquitoes and in the intestinal contents were identical in nature, and that they were the acting cause of yellow fever, the following working theory of the fever could be formulated. At first a subcutaneous introduction of the bacilli by the gnats (which might have derived them from patients or by feeding on other, *e.g.* faecal, material); affection of the superficial lymphatic glands (in which case the infection would seem to take place more frequently in the upper than in the lower extremity, as judged by the intensity of the lesions in the glands of the former); generalization through the system, giving rise to the influenza like first period of the fever; localization of the bacilli in and about the intestinal area, resulting in

absorption and distribution of toxic products causing the symptoms of the second period of the fever. It may be remarked that many writers (FINLAY and others) have laid stress on the difference between the onset and the second stage, and have variously suggested that the latter stage is due to some different cause from the first. Although symptoms of a severe character might arise from the elaboration of the specific toxic products in and about the gut as a consequence of a localization from a generalized infection it would not follow that an original infection could be established by way of the gut (compare experimental feeding and injection of many bacteria).

Prolonged cases, such for example as No. XI (Synoptic Table), and others less prolonged are perhaps due to multiple infections during the period of the illness.

TREATMENT

According to the figures (*Pará Medico*, January, 1901, p. 70), five hundred and fourteen patients were treated at the isolation hospital for yellow fever or Hospital Domingos Freire, of these one hundred and ninety-three or 37·5 died. This apparently is a high mortality rate, moreover the figures cannot be judged directly for two considerations: first, a large proportion of the patients are only sent to the hospital late in the disease, and not infrequently in an almost moribund condition (a few have arrived at the hospital actually as corpses), so that the mortality rate is no satisfactory guide; and secondly, the five hundred and fourteen patients include *all* admissions to the institution, so that the death-rate of the yellow fever cases is still higher, especially from the bed cards in which cases of slight mild yellow fever are recorded as gastric or perspiration or malarial fever, as well as those indubitable cases of malaria in which we found the malarial parasite.

Theoretically, the treatment is a 'hydrotherapie;' water to drink (plain, or Vichy or Apollinaris), copious enemata of normal saline, and, if bad symptoms ensued, hypodermic or intravenous infusion. Practically, a number of drugs were given over and above an initial purge of castor oil and calomel; aconite, digitalis, and belladonna were favourites at the early stage, and lactate of strontium later, this was supposed to be 'good for albuminuria,' but it did not appear to have any effect. Cold baths or packs, too, were much used, and were regarded by us as heralds of a possible autopsy. In the uraemic condition hypodermic injections of trinitrine, strychnine, etc., were administered; it need hardly be said that they gave no highly favourable result.

Judging from results one has seen, and without any personal care of cases, it would seem that the most important thing in treatment is to keep the patients in bed, and not allow them to leave it any more than one would in a typhoid case. Next, if the patient became infected in the house in which he is laid up, he should be removed from it at once, so that he may not receive a constantly increasing supply of the infecting agent; it is only reasonable to suppose that what otherwise might be a

mild case may become extremely grave if further and repeated infection has been allowed to occur. But if removal is to be carried out it should be done at once, and if the patient has been ill for say four days, he should not be exposed to the risks of disturbance by removal. In a well-ordered town which it is desired to free from the malady, there can be no question that all cases should be isolated, and that isolation should be effected promptly if it is to be of any use as well as non-injurious to the patient.

It does not appear that drugs are of much value; for cases treated in this wise from the first are not saved from a fatal result, and it seems wiser to withhold from them altogether, with the exception of laxatives. It seems of importance to induce, or at any rate not to interfere with sweating, as by chilling the skin, cold bathing, and the like; I think that care should be taken to supply blankets and other means to avoid chilling, and especially application of vapour baths or warmth. Except agonal sweats, the fact that a patient is sweating greatly increases the favourableness of the prognosis. The administration of plenty of water, in the form of saline enemata, or, if necessary, directly into the system, seems good; whether the former should be given cold, as I have seen it employed, is perhaps a matter for grave doubt. The temperature was rarely a source of anxiety as such in the cases seen; if it can be reduced by inducing sweating without drugs so much the better.

There can be no doubt that the patient ought to be protected from mosquito bites, for by those of already infected insects he may have added quantities of the infecting agent, and also he may contaminate otherwise uninfected insects and cause danger to his neighbours.

Just as malaria has been stamped or rather died out in England without the disappearance of the *Anopheles*, or of any very direct attack against them, so yellow fever has been stamped out in places without dealing with the mosquitoes; thus, yellow fever does not appear in the British Guiana reports, and has practically been absent in Jamaica since 1897; again, instances are to be found in the southern part of the United States and Porto Rico. At the same time, it must be admitted that the method adopted in Havana by the Americans for yellow fever, and at present being conducted on the West Coast of Africa by our own countrymen for malaria, is by far the most reasonable method of clearing a neighbourhood of a gnat-borne pest, especially a town disease like yellow fever.

No prophylactic inoculation has as yet been discovered for yellow fever, though many have been vaunted. It is clearly too risky to make use of artificial gnat infections. The only scheme which suggests itself as practicable is on the lines of the useful modes employed in some diseases of animals (as rinderpest), in which a dose of infective material is given with a dose of serum of an immune animal (*i.e.*, blood of early yellow fever patient mixed with serum of a convalescent).

VI. NOTES ON POINTS OBSERVED IN YELLOW FEVER

A. Typical Bites

One of the cases seen in Cuba called our attention to a lesion of the skin which in our notes we referred to as 'typical bites.' These are small rounded rather purplish petechia-like patches some two or three millimetres in diameter, surrounded by a pale zone which makes them the more prominent; they are without local swelling. In Parà we have heard them called 'petechiae,' but on pressure they can be almost completely banished so that the chief part of the lesion is a vascular dilatation; also on the *post-mortem* table they are represented by palish rather violet patches which are not very prominent. In distribution they are found on exposed parts especially wrists and ankles, but not infrequently occurring as high as the elbow and up the leg. We met with an occasional case in which they were distributed more generally over the body; thus one case is noted as covered with 'typical bites'—on 'face, forearms, shins, and ankles, also chest and abdomen and a few on back, thighs free.' We rather tended to think that the prognosis was grave in cases in which they were abundant; this particular case recovered after a severe attack. It may be mentioned that the pauper in Parà is often not very thoroughly clad, and at night perhaps any part of the frame may be exposed to the attacks of mosquitoes. In general the face escapes so far as very obvious lesions are concerned, but close inspection sometimes shews quite minute punctiform dot spots (it may be noted that at one autopsy the cervical lymphatic glands were examined and found to be deeply congested and haemorrhagic) also with a circumferential pallor.

They do not occur always, probably in about a quarter of the cases (they are noted in twenty-three out of ninety-four cases). Besides this many patients are seen to have been freely bitten as evidenced by the lesions and complaints.

There are several questions of interest concerning these 'typical bites'; in the first place they were only observed in yellow fever cases, so that it may be presumed that they have something to do with the fever. If they are lesions caused by gnat bites are they due to the bite of a particular kind of gnat? As judged by the bites we received they are not caused either by *S. fasciata* or *C. fatigans*. Are they due to the bite of an uninfected gnat, in a person suffering from yellow fever in whom the vascular dilation and haemorrhagic tendency are present? The answer here is, I think, in the negative since the patients in the yellow fever hospital were abundantly bitten by the above kinds, but typical bites did not occur after admission as far as was observed; judging by the fewness of the cases of infection derived at the hospital and the late stage of the disease at which the patients were often admitted, the gnats about the place were probably mostly uninfected.

The conclusion which we thought probable was that they were the local lesion caused by the introduction and local development of the parasite of yellow fever, and that the condition found in the lymphatic glands was of the same nature. The mode of proof by watching the progress of the bite of an infected gnat upon an experimental case could not be made, and unfortunately the Commission under Major REED do not refer to the matter.[1] Another mode of proof was by determining the presence of the yellow fever parasite in the locality. After scrubbing the skin with lysol and then with spirit, the spots were stabbed with a lancet, and the blood, which freely exudes, was taken directly into a fine sterile capillary without touching the skin. Examination of specimens thus taken were examined in the fresh state, and also stained with carbol fuchsin. In the stained condition a few small, fine bacilli from 2 to 6 μ in length were found in scanty numbers, sometimes in tiny groups of four or five, sometimes singly ; besides these bacillary forms sometimes small coccoid bodies in pairs or singly could be found. It was suggestive that these might be the spherical shape assumed by the bacilli in consequence of the bactericidal action of the blood, especially from the specimen of a late case (*P.-M.* 11), who had many typical bites when admitted on the fifteenth day ; in these some little groups contained, apparently, stages between the complete bacilli and the coccoid forms. Here there is, of course, a risk of contamination with skin microbes. At a later date after my illness I examined some bites (which were rather swollen and due to the entrance of several *C. fatigans* during one night through neglect of closing the mosquito net) ; the blood obtained contained many 'polynuclear' leucocytes, in some of which ingested bacilli, similar to our small bacillus, were found, as also in the salivary sacs of the gnats themselves ; this was very suggestive of an introduction of bacilli by the gnats (Fig. 2).

B. LYMPHATIC GLANDS

Since it appeared likely that the infection of yellow fever was introduced by some such agency as the gnat, it was possible that, the infection being local and superficial, there might be some signs of lesion about the corresponding superficial lymphatic glands. Our attention was more particularly attracted to this point by the marked enlargement, deep congestion, and juiciness of the axillary glands in our fourth autopsy, on October 29, 1900. After this, the investigation of the axilla became a constant feature of the clinical examination of patients; in some cases the inguinal and femoral regions were also felt, but comparatively little attention was paid to these owing to the obvious source of fallacy during life.

In forty-four cases of undoubted yellow fever, palpable and marked enlargement of the axillary glands is noted thirty-nine times, questionable enlargement three times,

1. It is obvious that if a single bite has caused the disease, the lesion, even if 'typical,' might be overlooked. I must frankly own that I should have anticipated finding the small bacillus in greater numbers in the axillary glands.

and no palpable glands only twice, in one of which the inguinal glands were also negative; of the other there is no note. Of twelve doubtful cases, axillary affection was noted in eight, and none in the remainder. In a number of other cases in which malaria was present, it was suspected that yellow fever infection was also at work. At the general hospital a number of odd cases were examined, as a rule these were negative; however, one batch of seven malaria cachectics gave two with glandular enlargement, one unilateral and one bilateral.

The general plan of palpation was to raise the arm from the side and thrust the fingers as high as possible in the axilla, put the arm to the side, and gradually work downwards. In some cases the enlargement was only on one side, in others on both; in a few cases there was distinct tenderness, but on the whole this was unusual. My colleague made observations on a number of cases from day to day, but the records of these have been lost; the general result was that the glands diminished and became unpalpable as the patient recovered. (One record in the notes gives enlargement on the fifth and eighth days, which had lessened on the tenth, and disappeared on the twelfth day). In my own case I have distinct recollection of finding distinct enlargement on one side about the first or second day; after convalescence there was nothing palpable. I may note here that previously, on October 23, I noticed that my right bicipital gland was enlarged and tender, and remained so for a few days, there was not sufficient general disturbance to take the temperature; it was ascribed to the effect of a mosquito bite without marked primary lesion. Supposing that this really was an extremely mild yellow fever infection, it would account for the mildness of the attack which I had some months later, when my comrade—certainly infected at the same time, as he was taken ill less than twelve hours after me—had so severe an infection. At the same time it may be mentioned that we met with a few cases of husband and wife in which both were taken ill on the same day, and yet the one died of acute yellow fever whilst the other had so slight an attack that without the circumstantial evidence it would hardly have been possible to make a diagnosis. Naturally, in these questions individual susceptibility cannot be entirely discounted.

The following is a summary of the conditions found at autopsy :—

Post-Mortem	Axillary	Femoral	Mesenteric *
4	Marked large. Deeply congested. Very juicy.	Seem large. Rather pale. Juicy.	Swollen and pink.
5	Large and massy. Not markedly injected.	? Enlarged.	Large and pink.
6	Much enlarged. Dark, congested. Juicy.	Large. Pale. Juicy.	Not particularly enlarged. Pale.
7	Much injected. Much enlarged.	Large. Juicy. Pale.	No note.
8	Enlarged. Injected.	Large. Pale.	Rather large. Pink.
9	Much enlarged. Deeply red.	Seem large. Not reddened.	Large. Pale.
10	Large : Somewhat reddened.	—	Not apparently large.
†11	Markedly large : Rather red.	Large, but not injected.	Larger than normal. Some much reddened.
†12	Markedly large. Some deep red.	Large : Somewhat reddened.	—
13	Marked large and red.	Apparently large. Not much injected.	Very distinct, and mostly much reddened and large.
14	Much enlarged and reddened.	Perhaps large. Pale.	Rather large : Not very red.
15	Large : Rather red.	Rather large.	All much enlarged, and rather pink.
16	Much enlarged and very red.	—	Enlarged, and rather pink.
17	Much enlarged. Deeply injected.	—	Large.

With regard to the enlargement and sometimes intense inflammatory condition of the axillary glands, it may be that it is solely due to the irritation of poisons (or bacteria ?) introduced by gnat bites, independent of yellow fever, or that it is due to the absorption of the specific cause of yellow fever. The principal locations of gnat bites may be said to be the hands, head and neck, and the ankles ; it is curious to note that in our autopsies the femoral group of glands were never injected with the intensity seen in the axilla and neck.

* Berangen Ferand says that enlargement of mesenteric glands in yellow fever is due to typhoid infection (*Traité de la Fièvre Jaune*, p. 61. Paris, 1891) : if this were the case we could hardly have failed to cultivate the typhoid bacillus, or to have some typhoid ulcers.

† In these two the cervical glands were looked at, they were very deeply reddened, and some had haemorrhages.

Naturally if there is any specific connexion between the glandular enlargement, which may be felt clinically, and yellow fever the point might be of diagnostic value. In Parà it was not possible to make satisfactory control observations ; especially in mild cases of fever, in the absence of any distinguishing mark, the discovery of enlarged glands did not lead to help—many such not included in the figures given above were seen. One question upon which no information was forthcoming is what is the condition of the palpable glands in malaria ; since being in Parà I have asked a number of physicians who have had considerable experience of malarial cases, but the axilla never appears to have been examined. In respect of this the following quotation may be of interest. A. C. SMITH[1] says :—'My attention has been attracted a number of times within the past dozen years to a group of symptoms which I have never seen described in any text-book . . . The group consists of inguinal bubo associated with malarial fever ; the bubo being most commonly non-suppurating and the fever of the aestivo-autumnal type, though not invariably so. The bubo, in the cases which I report, occurred without suspicion of venereal infection and was clearly secondary to the fever and dependent upon it.' It may be remarked that the author speaks of the inguinal and not femoral glands.

Information and observation then is wanted in non-malarial and non-yellow fever localities which are mosquito ridden, and also in malarial neighbourhoods which are free from yellow fever.

C. URINE

In conversation whilst in Cuba, I think Major REED mentioned to us that they had sometimes succeeded in finding tube casts in the urine, although, chemically, the presence of albumen was not apparent. We noticed that reaction for albumen could, sometimes, be obtained by the use of picric acid when other reagents failed. About ten days after my recovery, I found that, although no reaction was obtained with nitric acid, boiling, and the like, a distinct precipitate which did not clear up on heating was obtainable with picric acid. (When very small traces are tested for I fancy that it would be best to heat the urine before, rather than after, the acid has been run on, for the agitation prevents the formation of a ring.) Thinking that, perhaps, this result might be due to the presence of some proteid of a soluble nature such as a proteose, a number of specimens from patients were examined. The following are instances of the results obtained :—P. well-marked, rather acute yellow fever. Sample of urine boiled with drop or two of acetic acid, coagulum allowed to settle. When cool, filtered. Filtrate gives a good ring with superimposed absolute alcohol, on shaking this it dissolves. Addition of an equal volume of absolute alcohol (ethylic) does not give a permanent precipitate, which only commences when two

1. A. C. SMITH. *Inguinal Bubo as a Complication of Malarial Fever. New York Medical Journal*, LXXIII, June 22, 1901, and *American Medicine*, vol. II, no. 1, p. 38.

volumes have been added; three volumes give increase of the precipitate. The clear filtrate from this still gave slight haze with more absolute alcohol. This precipitate was collected and found readily soluble in water; the solution gave xanthoproteic reaction with nitric acid and ammonia strongly, and with weak copper sulphate and caustic soda a pink biuret reaction was obtained.

F, E, fatal yellow fever; three days before death. Urine loaded with albumen; in this case no acetic was added before boiling, otherwise similar procedure, the precipitate resulting from large addition of absolute alcohol (four volumes) was collected with the centrifuge and dissolved in a small quantity of rainwater. Clear yellowish solution, frothing on shaking, obtained. This, like the original filtrate, gives no reaction with boiling, with or without acetic or with nitric acid. With picric acid, and with acidified corrosive sublimate precipitation occurs; also concentrated ammonic sulphate and saturated sodium sulphate, when acidified with acetic acid, both give a good ring. It also yields a strong xanthoproteic and beautiful pink biuret reaction.

In other cases saturation with ammonic sulphate was tried in order to precipitate the presumed albumose, after boiling with acetic acid and filtering. In order to avoid the urates the crystals of the salt were generally added, gradually, with intervening filtrations; on testing the filtrates with nitric acid and ammonia, an orange xanthoproteic reaction could be obtained until the point of complete saturation.

Owing to the pigmented urates, and often biliary pigments, much difficulty was experienced; still in some cases the resulting final precipitates when dissolved in water, besides giving a good colour with nitric acid and ammonia, sometimes gave a pink colour with the biuret reaction. Picric acid also gave precipitates, permanent on heating; whilst boiling, with or without acidification, nitric acid and potassium ferrocyanide and acetic all failed to give signs. A number of attempts, such as the use of saturated ammonic sulphate, were tried for clinical purposes, but the large amount of urate present, especially in acute cases, shewed that these means were valueless.

In conclusion, it may be said that a more soluble form of proteid appears to be present in the urine in yellow fever. This is precipitable by higher grades of alcohol after the removal of the less soluble proteids, if present, and is also thrown down by ammonic sulphate in saturation. Unless it is some alteration product of the more precipitable proteids, it appears to belong to the proteose class; it remains in the urine after the more precipitable proteids have ceased to be passed, and also occurs in slight cases in which there is never any or only slight traces of these bodies. The use of picric acid and heat seems the best mode of showing its presence for clinical purposes. How far it can be used for the differential diagnosis of yellow from other fevers must be left to the future.

When the urine contains large quantities of albumin, the simple addition of acetic acid or a few crystals of neutral salt as sodium sulphate will bring down much

precipitate. The amount of coagulable proteid in almost any very severe case is extraordinary ; by the simple application of heat the solidification is often so great that the test tube can almost be inverted with safety.

Ehrlich's 'diazo' reaction. ALBERTINI,[1] from an examination of one hundred and forty-two cases of yellow fever, found the reaction negative in one hundred and thirty. The test being made from the second to the tenth day of illness concludes that the reaction is not given in simple cases of yellow fever.

Dr. MYERS tested a number of cases, chiefly at the earlier stages of the fever, also with negative result ; some further cases which were examined also gave negative reactions during the first week. In two cases in which there was malarial infection and possible yellow fever as well persistently gave positive reaction up to the twenty-fourth and twenty-eighth days. Two cases of yellow fever, in which there was prolonged jaundice, gave a fine deep-purple on the addition of the sulphanilic mixture ; this gave place to a good crimson on adding ammonia. Another case, with highly icteric urine, gave a deep-claret colour, which bleached to a dirty brown with ammonia. Several other deeply jaundiced urines failed to show either of these phenomena ; it may be added that many urines were tested at the same time so as to control one another ; a dozen malarial cachectics also gave negative results. It may be concluded that the test is of no value for the diagnosis of yellow fever.

D. KIDNEY, SPLEEN, ETC.

Kidney. The histological examination of the kidneys of the specimens is rather suggestive that the anuria is caused by an actual plugging of the tubules, and the hyaline class of cylinder seems to be especially abundant in the cases where the bladder was noted as absolutely empty at autopsy. In other instances (as No. 11), where the bladder was found full, although there is much disorganization of the kidney cells and a good deal of granular contents in the tubules, there was a marked paucity of condensed material in the form of definite casts. The casts seen at the bend of the Henle's loops look particularly likely to become hitched and cause obstruction. Moreover, the tubules and capsules shew signs of dilatation, as if there had been distension of a mechanical nature; and compared to a specimen hardened under the same conditions, in which the cause of death was due to some kind of focal liver infection and not yellow fever, and in which there was no kidney mischief, the glomeruli seem plump and nearly fill the capsules, the glomeruli in the anuric yellow fever cases are shrunken and withered and their nuclei often irregular. Whether, when anuria sets in, it would be possible to dislodge the plugs by some method of massage, so that they might be assisted to pass along the tubules, and whether too much bruising would be caused by such treatment of an already damaged organ, the

1. Albertini, *Rveista de medicina tropical Habana*, vol. I, 1900, p. 86.

extreme hopelessness of the condition might make it worthy of a trial. At the same time free and copious administration of water in the form of large subcutaneous or intravenous injections and enemata would be requisite to induce a flushing of the tubules if possible, and also vapour baths or 'hot pack.'

Spleen. The spleen does not appear to have been much examined in yellow fever. At all our autopsies with the exception of the four with malarial condition, the spleen was plump and turgid, though not enlarged; on section it was dark and usually much blood exuded. Microscopically the marked feature is the large number of large active macrophage cells[1] in the pulp; some much vacuolated and mostly containing remnants of nuclear material. It is clear that some great destruction is proceeding. Another feature is the condition of the adenoid tissue around the smaller arteries. I have to thank Dr. GLYNN for the loan of a normal specimen for comparison, and his kindly afforded experience. In many places the small arteries are devoid of any adenoid sheath; in other places where it is retained the borders are more ragged and less well marked than in the normal organ; at the same the lymphoid tissue is much invaded by macrophage cells mostly filled with vacuoles, hyaline pieces, and nuclear remains. Curiously enough here and there these cells have distinctly ingested lymphocytes, of this there can be no doubt where a distinct vacuole surrounds the ingested structure. In the normal organ a few relatively small macrophages are to be seen, but they do not shew the activity of those of the yellow fever cases.

Liver. The chief point of interest, beyond the fatty and atrophic changes which have already been described, is the frequently large number of leucocytes, especially 'polynuclear,' in the capillaries of the liver. The same is true of other organs, kidney and spleen, but perhaps not so striking.

Blood. It is stated in many books that there is an early yellowness, which is due to the presence of dissolved haemoglobin in the blood plasma. My colleague undertook the spectroscopic examination of the numerous serum and citrated plasma samples which we obtained in the course of our centrifugalizations for microscopical purposes. At no stage of the disease, early or late, was there the slightest indication of the oxyhaemoglobin bands. We concluded, therefore, that the so-called 'haemopoiètic' icterus was not due to the presence of dissolved haemoglobin.

Another statement is to the effect that the blood of yellow fever corpses does not clot well. We found that the blood taken into test tubes from the heart at autopsies made *immediately* after death clotted perfectly well and firmly; we supposed that, possibly, the statement originated from the observation of blood which had been exposed to *post-mortem* change within the vessels, and to the action of various bacterial invaders.

With regard to the counts which were made for determining the abundance of leucocytes in the peripheral blood, it can only be said that there is a marked

1. Many of these contain granules giving the blue iron reaction with potassic ferrocyanide and acid.

leucopenia or scantiness of leucocytes in the end agonal stages of the disease, this seemed to be an indication for the worst prognosis. The leucopenia probably, mutually, explains itself, and the great abundance of leucocytes found, *post-mortem*, in the vessels of the internal organs.

E. Cases of Illness at Instituto Lauro Sodre, and our own Infection

Case A. Little boy had occasional attacks of fever; these were stated to occur each month, according to the moon; prophylactic quinine was given a few days before full (? new) moon; no precise examination was made; the child seemed somewhat anaemic, compared to his twin brother.

Case 1.	Sept. 11.	Febre de transpiracao o da acclimitasao.
„ 2.	„ 15.	Yellow fever.
„ B.	„ 20.	Quartan malaria.
„ 3.	Oct. 1.	Febre amarella gastrica.
„ 4.	„ 17.	?
„ 5.	„ 18.	Febre amarella.
„ 6.	„ 28.	Recurrent in bed several days.
„ 7.		About this time in next chalet to ours.

On July 16 a man died of yellow fever; he was an occupant of one of the chalets; we were not able to obtain many details, so that the question whether he could have formed the original infecting case could not be determined.

Case 1. Robust middle-aged woman; arrived from France, September 1, 1900; came straight to Institute; lives in room at stables, without any civilized conveniences; has not used a mosquito net; takes meals at chalet G. with the G.'s.

Sept. 11. Quite well at 9 p.m.; taken with some shivering about midnight; vomited bilious matter, and severe headache.

„ 12. Severe, intense frontal headache; no pain elsewhere; facies, nil; chest, nil; abdomen, nil; tongue, flabby; skin, moist, sweating, slightly; temp., 38·7°; pulse, 118. 4 p.m., headache still severe; pain and tenderness at epigastrium; pain in loins and calves; face a little flushed, but no marked facies or thoracic injection; rather intense photophobia; tongue, furred; skin, hardly moist; vomit, yellowish, with a good deal of mucus; no ague parasites could be found in blood films; temp., 37·6°; pulse, 108.

„ 13. Headache less; skin moist; no icterus; no conjunctival injection; no pain; no vomit; complains of weakness; temp., 37°, pulse, 84. Evening, temp., 37°, pulse, 98.

„ 14. Some headache; no icterus; tongue, slight fur, edges red; papillae swollen; tenderness and pain at epigastric angle; no albumin (boil and nitric); temp., 37°; pulse, 98.

„ 15. No icterus; no fever; no albumin; gums rather swollen.

Case 2. Live in chalet G. This chalet is very full of mosquitoes, partly *S. fasciata*, chiefly bred in the ant guards of the pillars supporting the house, and partly with *C. fatigans*, probably from the stables. Arrived in Parà from France, July 14, 1900. (Two other occupants of the house arrived in April; they were not attacked); sleeps with inefficient mosquito net.

Sept. 15. Taken suddenly ill in evening; at 8 p.m., temp., 40°.
„ 16. Face and eyes injected; skin, flushed; no headache or pains; no vomit; skin dry; tongue, central fur and very red edges; no icterus; no albumin; gums not swollen; slight injection of fauces.
„ 17. Still flushed; hardly conscious; some albuminuria; no icterus; spleen and liver, nil.
„ 18. Still flushed; temperature falling; fair quantity of albumin in urine; no icterus.
„ 19. Feels better; no icterus; gums not swollen.
„ 20. Some epistaxis; gums slightly swollen; (?) slight conjunctival icterus.
„ 21. Some epistaxis; gums much swollen.
„ 22. No epistaxis; bleeding now from gums.
„ 23. Distinct conjunctival icterus; gums bleeding; albuminuria.
„ 26. No icterus; feels weak.
Oct. 2. No albumin; appetite returned.

Case 3. Middle aged, hearty but spare; cowkeeper, lives at stable; takes meals in chalet G. Arrived with wife from France and came straight to Institute.

Oct. 1. Taken ill in the afternoon; temp., 39°.
„ 2. Complains of frontal headache and lumbar pain; temperature normal; no sweating; examination of blood for ague parasites negative; spleen and liver, nil; eyes rather injected.
„ 3. Eyes injected; epigastric pain and frontal headache; tongue, much moist white fur; no icterus; much bilious vomiting; no albuminuria.
„ 4. Headache persists; no icterus; bilious vomiting, returns all ingesta; abdomen not tender; tongue, much white fur; acute epigastric pain relieved by vomiting; much albumin in urine; blood examination negative.
„ 5. Less pain; abdomen rather tender; insomnia; much albumin; no vomiting; no icterus
„ 6. Pain slight; generally better; albumin moderate; no icterus; weak and emaciated. Further history: no icterus; no haemorrhage; gums, nil.

Intermediate between these two cases a labourer living at the further end of the grounds was taken with fever. After four days, when the effect of the quinine which he had taken had passed off, quartan parasites were found in his blood.

Case 4. Brazilian, has lived many years in Rio de Janeiro. Twelve months ago spent some months in Europe, on account of severe attack of fever (malaria). Has lately been paying a good deal of personal supervision about the cowsheds and stables.

Oct. 17. Taken ill, the symptoms commencing in the morning; the attack ascribed to going out the previous evening without a hat. Lay down for a while before dejeuner, at which meal ate nothing, as everything 'tasted nasty.' Soon after had a shivering fit, and about noon temperature was 40°, there was some sweating; the temperature was taken at frequent intervals, and remained about 40°. At 6 p.m., temp., 39·7°; pulse, 114; face, pale; hot dry skin; no pain; no cough; no vomit; no diarrhoea; on the left wrist were noted five neat mosquito bites (rather typical).

„ 18. Morning temperature, 38·5°; rather uneasy mentally. 5 p.m., temperature 40°, pulse, 100; no icterus or vomiting. On this as on the previous day we desired to test for albuminuria but, promises notwithstanding, we could not obtain a specimen.

„ 19. The fever has abated to about 38°; no icterus. Patient was weak and pulled down and returned to his ordinary occupation about the twenty-fourth.

(About ten days later—October 28—patient's wife was laid up for a few days, but probably no importance should be attached since this was the case intermittently, chiefly, apparently, on account of the climate, which generally does not cause European women to thrive.)

Case 5. Female Portuguese (25). Arrived in Parà, July 17, 1900, and has lived all the time at the Institute.

Oct. 18. Taken suddenly ill; much headache and photophobia; bilious vomiting; temperature, 38·5°. The temperature was above 38° for the next two days; on the twentieth and twenty-first there was slight albuminuria; on twenty-second temperature fell to normal. There was no icterus.

About this time, or a little later (dates and notes lost) another Portuguese (case 7) was ill with a passing attack of fever, of undetermined nature. Our Chalet was situated between that of the last patient, this patient, and the Chalet G. We watched the course of the attacks with some interest, as it might afford interesting data concerning the spread of yellow fever. It came out that in the month of July, 1900, an occupant of one of the chalets had had severe yellow fever, and had died during transference to the yellow fever hospital. Before discussing further, it may be stated that no *Anopheles* were discovered about the institute; the nearest breeding-place that was found was three-quarters of a mile away. Except cases A and B, moreover, probably none of the cases were malarial. Case 5 is of interest from the malarial history, but I think that, probably, his illness was yellow fever of a typical character as occurring in an 'immune,' especially from the slowness of the pulse (*e.g.*, 114 when temperature was 39.7 = 103-4° fahr., and again 100 when temperature was 40 = 104° fahr.); there was no anaemia such as was observable in many other slight malarial attacks, nor were there subsequent fever attacks; lastly, there was no actual intermittence of fever or typical ague attack during the illness, which lasted but a few days. With regard to Case 2 there can be no doubt that this was yellow fever, and

the diagnosis of Case 3 as yellow fever can also hardly be questioned. Case 4 has already been discussed; Case 5 was also, probably, mild yellow fever, and was diagnosed as such at the Hospital.

Although it is not clear where the original infection came from, and the records are imperfect, the mild case of fever (Case 1) is of interest, since this may have been the 'infecting case' for the husband (Case 3), with a twenty-day incubatory interval. The connexion between cases 1 and 2 probably must go back to the same source of infection. It is also of interest that, although the cases started in the chalets on the one side of ours and then appeared on the chalets on the other side, we ourselves did not become infected. It may be noted that we were generally away during the daytime, and therefore avoided the active time of the local *S. fasciata*, and at night were so efficiently protected by mosquito nets that we were hardly ever bitten at night by *C. fatigans* nor at dawn by *S. fasciata*.

Our own illness was so long after these cases that I do not think it can possibly have been directly derived from them. It happened that we projected altering our abode to the neighbourhood of the yellow fever hospital, chiefly owing to the rains and the deficient means of transport to and from the Institute. However, on January 10, we learned that one of the nursing sisters was laid up with yellow fever (from which happily she recovered), and about a week previously another sister had been laid up with a slight attack of fever 'which could not be yellow fever because she was a Brazilian.' We consequently judged that the hospital should be considered an infected house, and that it would be better not to transfer to its neighbourhood.

On the 14th we performed two autopsies (one on a yellow fever case and the other not); that day we remained to dine at the hospital, and returned to the Marco about 8.30 p.m., otherwise we had not been at the hospital after dark since December. Seeing that I was taken ill with a rigor and vomiting on the night of the 15th, I do not think it possible that we could have been infected owing to this exposure, for the incubation would have been very considerably less than forty-eight hours. Curiously enough, just four days before, I had been most of the day catching mosquitoes about the sewage outfall of the hospital; but as my companion had never been near the place, and was almost certainly infected simultaneously with myself, the infection cannot have been due to some bite received there. Most probably we must have been infected whilst about the wards of the hospital, or whilst at lunch some days before; if this is the case, the infection must have been during the daytime, and therefore by *S. fasciata*. It remains to be said that my colleague was taken suddenly ill on the morning of the 16th of January, and unhappily he went rapidly down hill, and anuria setting in, carried him off upon the 20th, notwithstanding the constant care of the GOVERNOR, Dr. PAES DE CARVALHO, Dr. PONTES DE CARVALHO, and the assiduous ministrations of the nursing staff.

F. Yellow Fever on Ships

S.S. 'D.' Arrived at Parà on November 25. Perfectly good health on voyage; none of the crew allowed on shore; the only things brought on board from shore were beef, fish, vegetables, and ice; all of this carried out from the city (about two miles away) by the tender; otherwise only discharge of the cargo has taken place, namely, into nine lighters. No water was taken on board.

On December 2, B. (third officer) taken ill; seen on eighth day; certain yellow fever; transferred to hospital.

On December 7, boy (mess steward) taken suddenly ill, with temperature of 104·5°.

On December 8, ordinary seaman taken ill with fever.

On December 10, second officer was not well, but no rise of temperature.

Owing to only receiving information concerning this just before the vessel sailed, these last three cases could not be examined; it was stated that none had any jaundice, nor did they have definite sweating attacks.

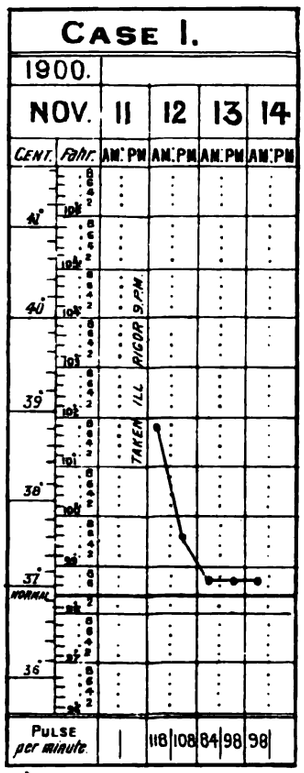
The vessel then proceeded to Manáos to discharge and receive cargo. It was stated that on the voyage up river one ordinary seaman was taken ill, but no details were forthcoming.

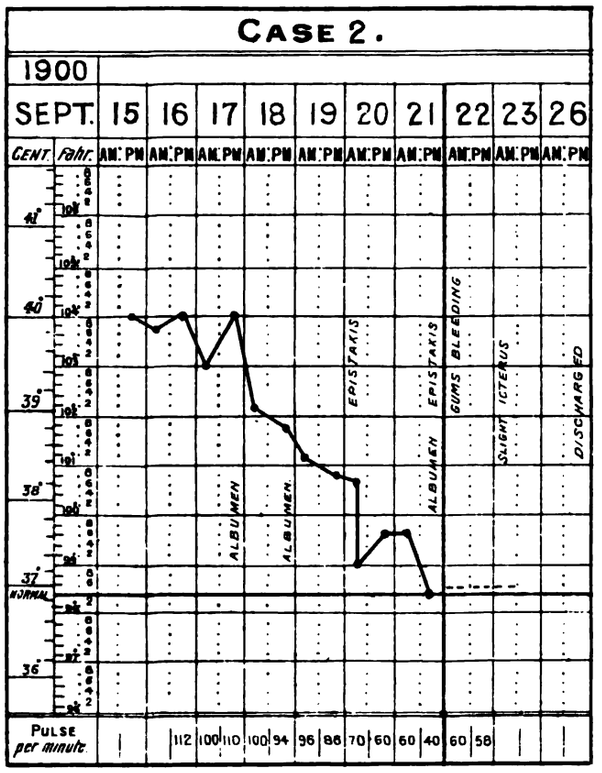
On leaving Manáos, D.I., a fireman, was taken ill on December 19. He was transferred to hospital on fourth day, where he showed symptoms of severe yellow fever (black vomit, bleeding from gums, delirium, icterus, prostration, and large quantities of albumin in the urine).

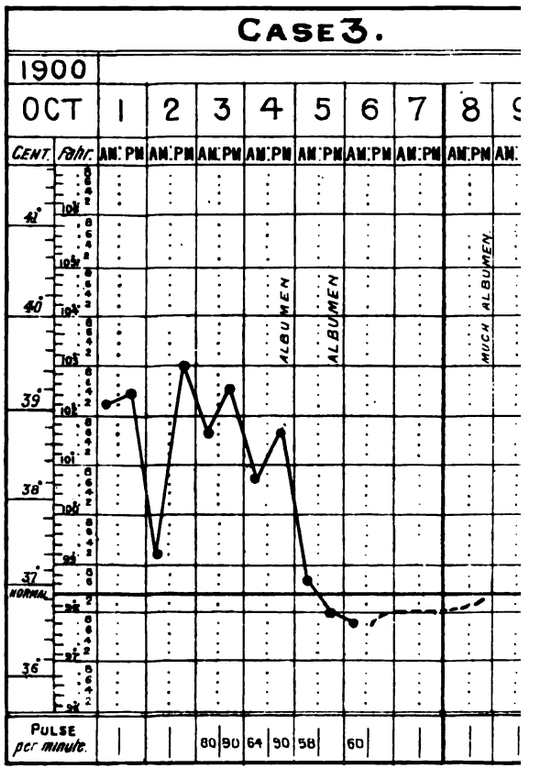
S.S. 'H.' Two men (third steward and a fireman) were taken ill on leaving Manáos, where the vessel had been for twelve days, on February 24, 1901. The former had a well marked moderately severe attack of yellow fever; the other gave a history of bilious vomiting, but on admission to hospital, on March 1, no definite symptoms of fever could be detected.

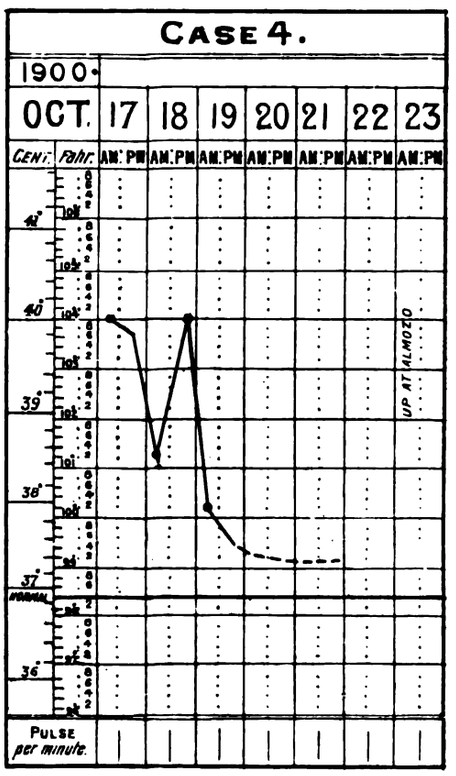
In the case of the steamer 'D,' it is certain that at least one case of yellow fever developed on board in a person who had not been within about two miles of the city (Parà). The only possible modes of convection of the infection would be (1) the food brought off, (2) the contact with the labourers who came to discharge the cargo, (3) infective material brought off in the tender or lighters, other than the items mentioned in (1) and (2).

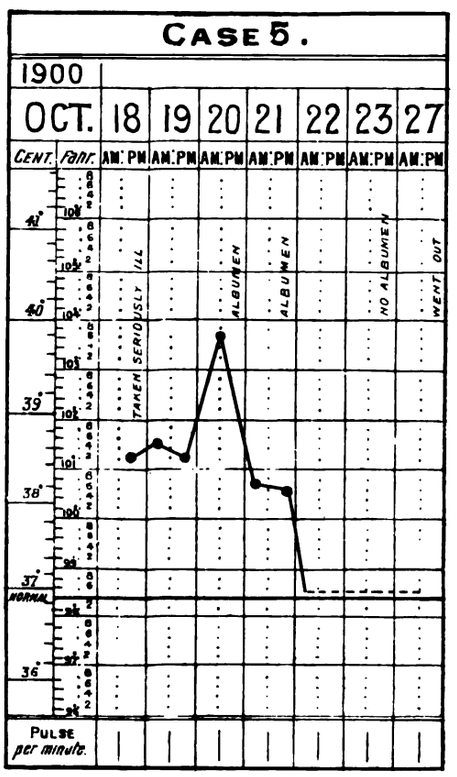
The first two points may be discarded, for it is unlikely that so few out of a population of thirty should have been taken ill if infected food had been the cause; in regard to the second heading, we know that far more intimate contact (*e.g.*, handling yellow fever patients or performing autopsies) than would occur under the conditions is not able to confer the fever.


CASE 1.
1900.
NOV. 11 12 13 14
CENT. FAHR.
AM. PM
TAKEN ILL RIGOR 9 P.M.
PULSE per minute.
118 108 64 98 98


CASE 2.
1900
SEPT. 15 16 17 18 19 20 21 22 23 26
CENT. FAHR.
AM. PM
ALBUMEN
ALBUMEN
EPISTAXIS
ALBUMEN
EPISTAXIS
GUMS BLEEDING
SLIGHT ICTERUS
DISCHARGED
PULSE per minute.
112 100 110 100 94 96 86 70 60 60 40 60 58


CASE 3.
1900
OCT 1 2 3 4 5 6 7 8
CENT. FAHR.
AM. PM
ALBUMEN
ALBUMEN
MUCH ALBUMEN.
PULSE per minute.
80 90 64 90 58 60


CASE 4.
1900.
OCT. 17 18 19 20 21 22 23
CENT. FAHR.
AM. PM
UP AT ALMOZO
PULSE per minute.


CASE 5.
1900
OCT. 18 19 20 21 22 23 27
CENT. FAHR.
AM. PM
TAKEN SERIOUSLY ILL
ALBUMEN
ALBUMEN
NO ALBUMEN
WENT OUT
PULSE per minute.

In considering the last heading, the most striking objective feature is the transportation of gnats. All ship's captains are agreed that gnats come on board with the advent of the lighters, and the men on the tenders complain of the abundance at night when lying close to the wharfs. The species found on lighters were 'town' kinds—*S. fasciata* and *C. fatigans*.

It may be mentioned here that during my trip up the river to Manáos, all gnats which we caught (with the kind assistance of the officers and a fellow-passenger) were preserved day by day, and *S. fasciata* did not occur until the day after arrival off Manáos, when ten specimens were taken, presumably they came off the lighters. Only other species came on board during the passage.

Investigation of a number of lighters at Parà shewed that *S. fasciata* larvae were present here and there on the bilge of the covered lighters, unfortunately they had been recently cleaned out and painted, so that probably the larvae were unusually scanty. The open lighters, some of which contained a considerable amount of water, were free from larvae; this was ascribed to the fact that they are used for coal (also salt, etc.), and the contained water was covered by a thin film of tarry or oily matter. The adult insects, however, would have to become infected; if this could occur, from feeding on the labourers more widely spread and more frequent outbreaks would be probable on these ships. It seems more likely that occasional infected gnats might be carried from the city in the lighters or steam tenders to the ships. The local conditions are such that the mode of transfer of yellow fever by gnats, is highly probable.

Several cases occurred amongst the persons who brought out steamers for the river service; here, however, the vessels lay close up to the city, and the individuals in question were in the habit of spending time on shore, so that no satisfactory evidence is afforded of the mode of infection. In all these cases pertaining to ships it is difficult to get satisfactory accounts, and, moreover, by the time that reports are received too much delay has intervened.

Nothing very definite is afforded by the following instance of a sailing vessel from the point of view of mode of transfer of the fever, but it shews how severely a vessel may be attacked about Parà:—

The barque 'C.P.' arrived off Parà on December 22, 1900, from Antwerp, laden with rails and other cargo, such as cement, under the German flag. The captain and crew consisted of fourteen persons all told. The vessel lay off the city abreast of it, that is, a matter of a few hundred yards distant, until February 4, when she was taken alongside the wharf to load with ballast for a week. This and other information was kindly given me by the captain. Mosquitoes did not appear on board till about a fortnight after arrival, *i.e.*, about 1st of January. (When I visited the ship they were appallingly abundant—*S. fasciata* and *C. fatigans*). Crew only went on shore with boat to return at once, and were never on shore at night.

Case	When taken ill	When admitted to Hospital	Result	Diagnosis
	(Arrival at Para, 22. xii. 00)			
1—V.F.	12. i. 01	16. i. 01	+ 16. i. 01	Yellow Fever
	(Discharge of cargo into lighters began 15. i. 01)			
2—J.B.	15. i. 01	17. i. 01	Recovered	Yellow Fever
3—A.F.	18. i. 01	21. i. 01	Recovered	Yellow Fever
4—E.	18. i. 01 ?	18. i. 01	+ 22. i. 01	Yellow Fever
5—M.	19. i. 01	21. i. 01	+ 23. i. 01	Yellow Fever
	(Discharge of cargo finished 22. i. 01)			
6—T.	26. i. 01	31. i. 01	+ 1. ii 01	Yellow Fever
7—D.	28. i. 01	31. i. 01	Recovered	Yellow Fever
8—K.	3. ii. 01	6. ii. 01	+ 8. ii. 01	Yellow Fever
	(Went alongside wharf 4. ii. 01)			
9—W.	6. ii. 01	9. ii. 01	+12. ii. 01	Yellow Fever
	(Returned to mooring about 11. ii. 01)			
10—P.	18. ii. 01	21. ii. 01	Recovered	Yellow Fever
11—C.P.	23. ii. 01	25. ii. 01	Recovered	Tertian malaria and ?
12—S.M.	24. ii. 01	25. ii. 01	Recovered	Yellow Fever

The captain had an attack of yellow fever four years previously at Rio de Janeiro. The other hand (not included above) had also had yellow fever some years before. Most of the above cases occurred during my own illness; they were diagnosed as yellow fever at the hospital, and such notes as were made and the temperature charts agree with this. The last three cases noted (namely, 10, 11, and 12) were examined; both Nos. 10 and 12 were indubitable yellow fever, rather severe in type. No. 11, however, certainly had tertian ague, for the parasite was demonstrated in his blood; he neither had jaundice nor albuminuria. His personal history was that he had had yellow fever at Santa Cruz six years ago, and again four years ago; he denied having had ague, or that he had been at all ill during the last four years when his voyages were between Hamburg and North America. It is possible that the virulent infections which were occurring of yellow fever organisms may have roused up a latent old malaria infection, although his immunity was sufficient to prevent any marked sign of yellow fever. None of the rest of the crew showed indications of an ague infection.

S.S. 'A M.' arrived at Parà, October 8, 1900. The vessel lay close to the wharf, on the mud at low tide; the proximity to the city and the fact that the men went on shore prevents any direct information. The chief engineer died of an 'access of pernicious fever;' this occurred after about six or seven days of illness, and patient was very jaundiced at death as I was subsequently informed. The boatswain had a well marked severe attack of yellow fever, and a week later the third engineer was taken ill and died also of well marked yellow fever; it may be remarked that the diagnosis of 'pernicious access' is a not uncommon means of reducing the yellow fever mortality and increasing the apparent danger of the city.

Whilst isolated cases recognized as yellow fever occurred occasionally on the ships which do not approach close to the cities (Parà and Manáos), occasionally cases of slight fever occur, the nature of which is not clear from the accounts which can be obtained of them. One case, which was seen a week after being taken ill, may be cited. S.S. 'L.,' steward taken suddenly ill with a rigor, the thermometer shewing 103° F.; he was treated with a purge and quinine; the next day there was still fever, and the hands and up to the elbows were described to have become swollen, 'like dropsy;' on the third day this swelling went down, and patient was feeling much better, but very weak; at the end of a week the only complaint is of weakness; there are no objective symptoms, *e.g.*, icterus (unfortunately there was no means of testing the urine for albumin), except that the right axillary glands were palpably enlarged, and there were signs of many old bites about the hands.

VII. AGUE AT PARÀ AND HABITS OF *S. FASCIATA* AND *C. FATIGANS*

The species of *Anopheles* met with about the Amazon is one with white tarsi to its hind feet, the extreme tip of the foot being black; it is identified as *A. argyritarsis*.

It was intended to experiment with these in order to ascertain whether it was a favourable host for the gnat cycle of the ague parasites. Except at the commencement of our stay at Parà, it was difficult to obtain larvae or pupae in abundance, and at the time named we were too much occupied with yellow fever. Had we anticipated this difficulty it would have been well worth while to have sacrificed some time to the matter whilst the supply was abundant. It is, therefore, only possible to state that the houses near the breeding places where this species was found were all ague stricken; in some cases the presence of the ague parasite was determined in the blood of persons from such houses.

Two individuals of another species (*Anopheles lutzii Theo.*) were taken; this has unspotted wings and is all dark, with the exception of a dorsal longitudinal white line. None of the larvae from different pools hatched into this kind; its breeding places were not found.

The larvae of *A. argyritarsis* were found in small muddy pools a few inches deep, the largest pool was only about six feet by three feet. They were never met with in large or deep collections of water in pools containing obvious green algal growth. They are extremely active, and on the slightest disturbance seek refuge in the mud, so that it is possible to bale out much water with a small cup without catching a single individual unless some of the mud is scooped up. It was found in practice that a gauze net was the best means of catching them, the individuals being picked out with a wire gauze spoon; in this way one could avoid carrying much mud and predacious enemies, such as tadpoles and dragon-fly larvae. In all cases where *Anopheles* larvae were found they could be detected by inspection for a few minutes; I never succeeded in catching any with the net in pools in which they could not be detected by watching.

Observations on some pools in the proximity of some brickworks teach the lesson that the absence of *Anopheles* larvae in given pools may be temporary, and indeed, follow an extraordinary abundance.

Four pools in some sand diggings, close to some brickworks, were examined on many occasions. There were cases of 'seisoes' in nearly all the huts in the neighbourhood; two huts had all the occupants sick except one individual; one of these

huts was occupied by new-comers, (man, wife, and three children). Three of these were examined, and certainly were suffering from malaria, and the other two were also ill.

Pool 1. (About fifteen by eight feet), muddy, moderate amount of green algae ; one end shallower and eventually cut off during drier weather ; as seen when nearly dried out, probably deepest part when full not much more than a foot. Interval between Pools 1 and 2 = twenty yards.

Pool 2. (About thirty by fifteen feet), deep; very much green ; never dried out; water rather muddy. Interval between 2 and 3 = fifty yards.

Pool 3. (About six by four feet), shallow, not more than about 6-8 inches ; muddy ; no green growth. Interval between 3 and 4 = sixty yards.

Pool 4. (About twenty by twenty feet), rather muddy generally; red growth, sometimes intensely ruddy ; no green obvious more than one foot deep.

Pools 2 and 4, never yielded any *Anopheles* larvae.

When first examined about the middle of September, Pool 3 was thickly crowded with *Anopheles* larvae (= + + + +), none were found in the other pools.

Sept. 29.	Pool 3.	= + + + +	Pool 1,-0.
Oct. 4.	„ 3.	= Very scanty ; many water beetles.	
„ 10-16.	„ 3.	= Very scanty ; pool drying up.	
„ 19.		Extremely scanty ; pool much reduced.	
„ 23.	„ 3.	Dry ; other pools much reduced.	
Sept. 1.	Pool 1.	Few + especially at end cut off from general pool.	
„ 2.	„ 1.	As yesterday ; Pool 3 consists of a few hoof-mark puddles = 0 ; Pool 2, no *Anopheles*.	
„ 12, 13, 15		No *Anopheles*.	
Dec. 3.	Pool 1.	Few *Anopheles*.	
„ 7.	„ 1.	No *Anopheles*.	

It may be noted that these pools were much haunted by dragon flies, and there were many water beetles, and a 'white and dark' water boatman, the presence of which may account for some of the diminution or disappearance of the larvae ; *Culex* larvae were also present (= *Taeniorhynchus fasciolatus*).

The following localities shewed the presence of *Anopheles* larvae :—

At Parà. 1. Shallow muddy pools about brickworks near Travessa Bonifacio, already mentioned.

2. Shallow muddy natural pool (about six by three feet) below lower corner of Baptista Campos. Larvae scarce; a case of tertian fever was examined which came from a house not far distant.

3. Tiny natural puddles at the S. Jronymo end of Trav. 3 Maio; some of the occupants of the surrounding houses stated that there was 'much fever,' but no cases were actually examined; search for adults in some of the houses not successful.

4. Wheel track puddles of muddy water near house of Senor M., beyond Marco da Legua. A man was taken ill, in a hut a few yards away from the puddles, and shewed tertian parasites in his blood.

At Manáos. 5. Wheel track and natural puddles at Cachoeirinha, Manáos; all shallow and muddy, without green growth, but extending here and there into the grass (rainy season). This region has the reputation of being the ague locality in Manáos: it consists of a comparatively high-lying plateau away from 'swamps,' and, in a general way, does not look like a fever stricken place. On this plateau of a few acres extent, large numbers of *Anopheles argyritarsis* larvae and pupae were readily collected. One point of interest is that a few individual larvae were found in the pools on the course of what becomes a miniature torrent during a rain shower, and carries the water down to the igarapé (stream) some fifty or sixty feet below; from the steepness of the descent, and the small size of the puddles, and the direct evidence of drainage from *Anopheles* puddles on the edge of the plateau, it is most likely that these isolated single larvae were carried down from above.

From what has been said it appears that this species favours small very shallow pools; these consisting of opaque muddy water, and freedom from growth makes the larva a very conspicuous object to inspection. The small size of the pools makes them eminently suitable for filling in or for treatment with kerosene, etc., and whenever pools or collections of water were met with in or about the city they were always inspected, and often netted also, but the above-mentioned places alone yielded larvae; pools that were only observed once may have been temporarily in abeyance.

Dr. Furness, of Bahia, told me that he had met with the larvae (of the same species) in the 'ant-guards' in gardens. In Parà I did not meet with any in these water collections, although in one garden adult insects were met with and a natural breeding place was found not many hundreds of yards away (*B. campos*). Nor, again, were larvae discovered in swampy and overflowed districts in the forest and outskirts of the city. During the prolonged operations for laying a fresh tramway track there was much water lying about in the Estrada da Independencia for months, but these pools were not affected by *Anopheles*.

The adult insect as seen in 'bred' specimens is very sleepy during the daytime, it sits on surfaces in the 'correct' attitude, the abdomen being inclined at an angle of about 45° to the vertical. The hind legs and tarsi are generally kept close together, contrasting with the widely separated hind legs of the 'culices.' In two houses (one on the *Est Nazareth* and the other on the *B. campos*) adults were seen on the wing after dark, about 7.30 p.m. To my knowledge, I was only bitten by *Anopheles* on two occasions, once about an hour before sunset (about 5 p.m.), and again about an hour after sunrise (about 7 a.m.); there was no untoward effect. This is simply noted as evidence that this species may bite during daylight, at any rate at the beginning and close of the day.

By local repute there is much malaria at Parà; but out of the Englishmen and other foreigners that I met living in different parts of the city there was only one who had definite ague attacks, and he was in the habit of going out on expeditions, and did not trouble about taking a mosquiteiro. The fringe of the city bordering on the swampy low-lying regions are responsible for most of the cases. By reputation the more out-lying district, where the huts are right in the swamp, are bad for ague, but in general the dwellers, who were questioned in these parts, where the huts are some distance apart, denied that they had fever, and dredging and inspection of the overflowed ground failed to yield any *Anopheles* larvae.

Blood examination of cases about the city generally shewed tertian parasites; one case of quartan was seen. Crescents and so-called aestivo-autumnal parasites were more common amongst the cases coming from the islands; these persons were often in a most dreadful condition of extreme anaemia, their appearance quite waxy and almost translucent, their blood extremely watery, and shewing marked alterations of their few red blood corpuscles (macrocytes, microcytes, poikilocytes, and nucleated reds).

Positive diagnosis of ague by blood examination is by no means easy in the semi-civilized population of Parà. This, I think, is attributable to the wholesale faith in and use of 'Remedios,' and a case of illness of any kind which has not had quinine in some form or other is a rarity. The importance of distinguishing mild cases of yellow fever from ague was not appreciated, and notwithstanding oft-repeated requests to withhold quinine, often even in cases in which there did not appear to be any indication far less any necessity for the drug,* we generally had to be content with a negative examination, which naturally left the diagnosis uncertain. Diagnoses of malaria too help to lessen the yellow fever reputation of the city.

In some of the rubber-cutting districts in the swampy riverside forest there is much malarial fever. Arrangements were to have been made for us to visit some

* Thus one has seen quinine given to perfectly afebrile cases.

bad localities so that practical suggestions might be made to deal with the local conditions. However, this visit was put off. Unfortunately, however, no arrangements were actually made, and, therefore, no suggestions can be made. By repute several places which were very fatal to early pioneers are now regarded as comparatively healthy; even if this be true the possibilities are too numerous and vague to make discussion profitable.

Elsewhere the question of the clinical condition of the superficial lymphatic glands is raised, and it may be repeated here, since if enlargement does not occur, for instance, in the axillary glands in malarial, but not yellow fever districts, the point may be of some use in the diagnosis of yellow fever, especially in mild cases, and perhaps also in malarial individuals.

It may be of interest to mention that quite a number of Brazilians (medical and lay) hold that malarial attacks are apt to occur at monthly intervals, some even go so far as to consider that the moon is the directive force.

Some use was made of the centrifuge to assist in the discovery of malarial parasites. The scheme was to take about three volumes of blood into a capillary (such as one ordinarily uses for sedimentation tests) containing about one volume of citrated salt solution (one per cent. citrate of soda giving eventually one-quarter per cent., which prevents coagulation); after mixing well, the tube is sealed at the end, and centrifugalized for a few minutes. Three layers are obtained, supernatant plasma (with many suspended platelets), protoplasmic layer (containing leucocytes, platelets, and crescents), if present in the blood, red corpuscle layer. In a warm climate, if the tube is kept some time before it is centrifugalized, the leucocytes may have crawled about on the glass, and thus make an unduly thin layer above the red. By cutting off the tube just above the leucocyte layer, the leucocytes and upper layers of red layer may be removed with fine capillary and examined. For making permanent preparations, it is best to fix rapidly, as by placing the films at once into a petri dish into which a drop of strong formalin has been put; red corpuscles are apt to crenate more rapidly from the diluted plasma than from plain blood. The leucocyte layer forms an easy means of detecting pigmented individuals, and thus assisting diagnosis, and also gives concentrated specimens where it is desired to make differential counts of the varieties of leucocytes. We also tried using a fixing fluid for the dilution, such as saline solution, with a trace of corrosive sublimate, naturally the proportion of blood taken must be less, otherwise clotting will occur.

Yellow Fever and Ague. It has sometimes been stated that there is some antagonism between the two diseases. Out of our seventeen autopsies, in four cases there were malarial spleens; one of these is interesting, and is in accordance with the chances of infection. The patient was a Bolivian soldier who got malaria up river on his passage over from his home country; a few days after arrival in Pará he contracted fatal yellow fever. So far as Pará is concerned, an immigrant coming

into the city is likely to have yellow fever in mild or severe form first, so that by the time he gets malaria he has already acquired yellow fever immunity. There does not seem to be any indication of a mutual protecting power between the two diseases.

Stegomyia fasciata

Distribution. Common house mosquito about city and outskirts, as at yellow fever hospital, Hospital Santa casa, Marco da legua, Asilo dos alienados (Leper-asylum), also at Pinheiro (ten miles down river from Parà), and Outeiro. Also on vessels and lighters lying off Parà. At Manáos, in many houses about city and suburban region 'Cachoeirinha.' Never seen out in forest away from houses, or in isolated huts situated away in forest. Not seen at Santa Anna, some twenty-five miles north of Parà, or Fazenda Natal, in Marajo.

Breeding Places. Casual waters in vessels, etc., in and about houses such as buckets, tins, washtubs, rain gutters, ant-guards (perforated troughs to protect plants in gardens, and sugar, etc. in houses), larger and deeper collections of water as casks or hogsheads full of rain water. Also in bilge water of barges, lighters, and s.s. Viking (Amazon Telegraph Co's ship, many years on the river). Not found in sewage collections as cesspools, stable runnings, etc., although found in neighbourhood in cleaner waters. Also not found in natural puddles in forest or streets, etc.

Habits of Adult. This species in Parà is solely a day gnat. It consequently afforded means of observation. It is on the wing and will bite shortly after sunrise, (about six a.m.); again, a few have been observed biting about eight to nine a.m., after which there is a pause till about eleven a.m., when again a few may be feeding. The time of chief activity is in the middle of the day, from about twelve to two p.m., they then bite freely, and are seen to copulate on the wing in numbers; another pause follows, though there may be a few about, but they do not cause trouble when one is sitting at the microscope until about half-past three till about five p.m. After dusk or dark I have only once met with a specimen; this was a male, feeding in a sugar-basin rather before seven p.m. These statements are derived from observations whilst working in the laboratory, and during a residence for a week in the house of a gentleman, whose garden was liberally supplied with ant-guards (perforated troughs filled with water, for preventing the access of the destructive 'Saũba' to the plants), each of which was full of developing larvae and pupae. Sitting in the verandah of this house it was easy to catch fifty to eighty specimens without moving from one's chair, in the early hours of the afternoon, yet after sun-down, not a single individual was met with.

In so far as yellow fever infection is associated with this insect, it is of importance to note this in relation to the common idea that the fever is commonly caught at night. It would appear that night would only be dangerous from this insect in so

far as the first of the day after sunrise is included in the term 'night.' In this connexion it is of interest to note that all the artificial gnat infections carried out by the American commission were done during the day-time, *S. fasciata* being the species employed.* Besides feeding on man, I have observed it on dogs, on an agouti, and a bat.

The periodicity of feeding activity was more closely observed on this species, but I rather believe that a similar intermittence of rest and activity occurs with other gnats, 'night' as well as 'day' ones.

One batch of *S. fasciata* was put with a number of living butterflies, but they did not feed upon them ; on the assumption that night-feeding insects attack night-sleeping animals, and *vice versa*, an experiment with moths would have been more apt, but none were available at the time. It may be mentioned that the period of greatest activity of *S. fasciata* corresponds with the time of siesta of the human being.

On one occasion embryo filaria was found in this species ; the source of its infection was not found, but the suggestion is that it would have been a diurnal worm.

The eggs are not laid in an adherent raft ; they are practically separate, and are deposited close to the edge of the water, if not sometimes actually on the surface of the containing basin. At any rate, they readily adhere to this surface sufficiently firmly to prevent detachment by a stream of water ; this is probably of use where the breeding place (*e.g.*, a small tin or a roof gutter) is exposed to tropical rain.

The larva is easy to recognize from its curious opaque appearance ; unfortunately no description was made. As has been observed by Dr. FINLAY, of Habana, as regards spontaneous drying† I have seen almost full-grown larvae appear very shortly after putting water in a 'dried' basin in which development had been occurring. In two cases the time of cycle from laying of egg to imago was noted ; in one the first pupa appeared on the eighth, and hatched into a male on the tenth day ; in the other, the first hatch occurred on the twelfth day ; in both cases larvae continued to be present for weeks after the first hatch. (It need hardly be mentioned that the vessel was effectively screened against intrusion of other possible egg layers).

The adult insect varies considerably in size ; this is true of both sexes. When sitting on a vertical wall the abdomen is tilted towards the wall, so that the tail nearly touches it (*i.e.*, in the contrary sense to the orthodox *Anopheles* posture). The hind legs are separate from one another, and away from the body the tarsus curves downwards, but tends to a more or less horizontal position.

* It is, perhaps, unsafe to dogmatise absolutely that any gnat is purely a 'night' or purely a 'day' biter.

† N.B.—The atmospheric humidity in Para is never very far from the saturation point.

Culex fatigans. Wied

Distribution. This is the common house mosquito of the city, in this respect resembling *S. fasciata*, but differing in being a night insect; although found in and about the city and on lighters lying in the river. It was not very common about the Hospital Domingos Freire (yellow fever), and about the first occasion it was met with there was coincident with the occurrence of a spontaneous yellow fever case; *S. fasciata*, on the other hand, was abundant there. It was not met with in huts away in the forest; nor did it come on board the steamers while going up the river.

Breeding Places. This species seems especially to affect foul waters; larvae were found abundant in stagnant pools of stable runnings, and also in a cesspool, the covering of which was damaged. Larvae were not met with in puddles in the forest. All attempts to breed it from the egg in clean water in the laboratory resulted in death of the larvae a few days after hatching. In fact, it seemed to be essentially a 'filth' loving insect.

Habits of Adult. This species seems to be a purely night insect; often a crowd of males would appear just after dusk in our chalet. Numbers of females full of blood were easily obtainable in houses in the city. The eggs are laid in a raft of vertically disposed black eggs.

VIII. GENERAL HEALTH OF PARÀ

The city of Parà, or Belem do Parà, is situated slightly south of the equator (lat. 1° 26′ 59″ S., and long. 48° 30′ 0″ W.), and about seventy miles from the ocean. It is built on a tongue of slightly raised land, which forms a sort of flat ridge, at the end of which is the river front (Rio Guajara), and on either side are swampy, low-lying districts, into which the fringe of the city extends. The elevation, though very inconsiderable, is ample to give a very fair gradient for drainage; at the same time the soil consists of sand, and through this much of the fallen rain water soaks away, where from traffic, etc., there is no coating of mud. The tide helps to cleanse the river front, the rise at spring being about ten feet; but the wharfside bays are sufficiently sheltered from the current to allow the accumulation of much filth, in places a bed of mud being exposed at the fall of tide.

The general health and mortality in the city must be looked at from two standpoints, namely, that of the native and old resident and that of the newcomer. For the newcomer, as in other regions where yellow fever is endemic, is liable to undergo risks of becoming infected with this disease and to die of it; consequently, especially in times of considerable immigration of susceptible persons, the apparent death-rate is not a fair estimate of the mortality due to all the local conditions which affect the well-being of those who have resided long. There are no figures to show the extent of the yellow fever risk in Parà; but it is to be seen from the cases, with which we had to deal, that the city is extensively riddled with the disease, for we had cases from houses in all quarters, even out to the Marco da Legua ('a league from the city'). So that there was no part (at any rate during the later months of 1900, when the considerable outbreak of the earlier months was on the wane) which one could confidently state was free from risk. Many of the milder cases pass unrecognized, and perhaps not a few of the more severe pass under other names; the tendency in yellow fever districts is, for those in control, to endeavour to make as little as possible of the disease, 'so as to avoid giving the place a bad name.' Naturally nothing could better tend to foster the disease than such measures. The incidence of the fever on a given number of traceable individuals cannot always be given, but figures are extant in the case of an Italian dramatic company, which visited Parà in April, 1900, and shew that out of the company at least twenty-nine individuals became infected, and at least nineteen succumbed to the fever; these include not only the lower grade of artists, but also some of the more reputable.

Considering the situation of the city so near the equator, the climate is less hot than might be imagined; the almost daily shower of rain, be it 'dry' or be it 'wet' season, conduces to produce this result. But at the same time it gives rise to the

excessive humidity of the atmosphere which is so enervating to the northener. Local authorities love to quote the words of travellers who speak of the delightful freshness and coolness of Parà after being in the hot steamy interior, but they do not draw attention to the still more delightful freshness which is experienced in getting out to sea. The steamy heat reacts unfavourably on the energy of the native and foreigner, and makes the place rather unsuitable for the prolonged, continued residence of Europeans; so much so, indeed, that one of the leading physicians informed me that he always recommended foreigners coming from cooler climes to spend six months in Europe at least every three years, that is to say, a much shorter period than is customary in India and other tropical places. By heresay evidence I gather that some of the more successful business has been conducted by firms consisting of a number of responsible partners, each of whom is thereby able to spend comparatively short stays in Parà, and much time in Europe. Thereby a certain briskness and energy can be brought to bear in a manner which can hardly be expected from those who have made prolonged stays. So far as I was able to observe, the women from northern climes are particularly unable to withstand the climate; thus the wives of several residents have found themselves obliged to reside in Europe.

The general tendency to apathy and slackness is also due to the monotony of the conditions—uniformity of temperature year in and year out, no relief by change of season, except, perhaps, for the worse, during the so-called winter or wet season (January to May), when the humidity becomes still more trying, and the absence of recreation, so far as the majority are concerned. The business of one day ushers in the business of the next; and, on the whole, there is but little social intercourse. One difficulty in the way of obtaining recreation, which cannot be neglected in considering the opportunities for all, is the financial aspect. The price of things in Parà border on the absurd, especially when the rate of exchange is high; this makes itself felt, especially on those who receive a salary in sterling currency based on a certain rate, for instance, ninepence per milreis, a serious deficiency in the purchasing power of the salary, when the milreis goes up to twelvepence or thirteenpence per milreis, as was the case during my stay.

Some break or change can be obtained by residing out of the city, as for example, further down the river at Pinheiro (one hour) or Mosqueiro (two hours); but the service of steamers is slight, and arranged more for government office hours, which are not found particularly convenient for business purposes. On the land side, where the air is not so fresh and breezy (as especially about Mosqueiro), many people live out at or towards the Marco da Legua (the mark of the league distance from the city), to and from which they travel by an erratic and miserable tramcar service.

The action of the climate upon Europeans is probably enhanced by the performance of brainwork under high pressure, now and again with unexpected worry for

having to deal with childish interferences in the way of rules and regulations, formulated from time to time by the authorities. The hours of business are long, usually about eight or nine a.m. to four or five p.m., with a break for 'breakfast' about mid-day. Frequently for the despatch of mails, the heads or principals return to the office again in the evening till a late hour. When the mail happens to be despatched on a Sunday the opportunity for a week end out of town becomes impossible. One week follows another, year in and year out, much in the same way, until leave of absence comes round. There does not appear to be any general rule of any sort of annual holiday for a few weeks as in cool climes.

With sufficient wealth and independence, conditions of life are naturally much better; also at the other extreme, the labouring classes are better off, for wages are sufficiently high, and labour sufficiently scarce to make them fairly independent; moreover, they are not troubled with the wear and tear of exchange, the price of rubber and the like; and they are inured to the climate. The better class Brazilians in general are not particularly energetic, and many of them endeavour to make visits to Europe and the north for a change.

Diet. The food arrangements cannot be highly extolled, the chief difficulty being the scarcity and expensiveness of fresh vegetables. Beef forms the chief staple, and is raised on ranches in the neighbouring island of Marajo; a better quality is now and again brought up by cattle boats from the Rio Plata, whence also occasionally some mutton is brought. Fish abounds in the rivers and many kinds are delicate for the table, but there is no proper organized scheme of transport, so that it is liable to suffer before or soon after it reaches the market; I understand that an endeavour was made to start a reasonably conducted system of transport, but this was quashed by petty regulations. Fowls, ducks ('Muscovy ducks'), guineafowl, turkeys, etc., are also obtainable. Native animals, Páca gutia (agouti), tartaruga (water tortoises or 'turtle'), etc., are occasionally met with. A poor quality of bread is made from imported flour. Numerous kinds of vegetables for cooking or for salads are cultivable or native, such as sweet potatoes, mandiocca, beans, pumpkins, eggplant, mascisce (a small kind of cucumber), carurú (often used as a crisp salad), vineigreira (sorrel like), lettuce, etc; but the importation of potatoes, cabbage, onions, carrots, etc., from Portugal or the United States, saves the trouble of growing things locally. Some attempt has been made to introduce the cultivation of various northern plants, but seemingly no endeavour to improve or enlarge the supply of native products or of plants known to thrive in the climate has been made.

Of fruit also there is a considerable variety; besides bananas, oranges, and pine-apples, which ripen all the year round, and the avacate (alligator pear) and mango, which have seasons, there are a number of native fruit, many of which are peculiar to the region. Cupuassú, Bácury, Genipapa, Sapotilha, Abiu (Sapotaceae), Ata Biribá (Anonaceae), Caju (Anacardiun), Maracujá (passion flower), may be mentioned, some

being eaten fresh, others cooked or made into fruit drinks with the addition of water and sugar. Mention also must be made of the essentially Amazonian 'Assahy,' made from the fruit of the palm of the same name, by rubbing it with water and straining the resulting thick purplish emulsion, with a fascinating taste, which is taken with sugar and mandiocca (cassava) meal; a similar 'drink' is made from the bacaba palm but has not the same reputation for delicacy of flavour.

The common light wines of Portugal form a common addition to the meals. Abuse of alcoholic beverages (*e.g.*, whiskey) by Europeans is happily not a prominent feature of life in Parà.

The poorer natives and Portuguese are, in general, not given to great varieties of diet; besides the staple Farinha (mandiocca or cassava meal) imported dried salt codfish, imported rice, and imported dried beef (xarque), and dried beans, form the principle items. A large fish (pirarucu) is caught and dried and salted and used to a considerable extent, but is said to be less economical than the imported fish. The native alcoholic beverage is the spirit distilled from fermented juice of the sugar cane (caixaça or cachaça), and leads to a certain amount of intemperance.

Temperature. The temperature at Parà varies between a maximum of about 32° C to about 20° C (or in Fahrenheit scale, say 89·6° to 68°); during the five years 1896 to 1900* the highest recorded temperature was 33·5° or 92·3° F. During our stay we found the variation was between a day maximum of about 31°, rarely higher, occurring in the early hours of the afternoon, and a minimum of 21° at night during the 'dry season,' and 22·5° during the wet. The absence of really high degrees is probably due to the rain which falls almost every day in the afternoon during the so-called dry season, and the obscurance of the sun by the heavy rain or thunder-clouds. The rain showers are usually very localized, so that one day one part of the town or suburbs may escape, whilst the following day it may be the site of a heavy drenching; consequently the observations with a single rain guage give but slight ideas of the general rain fall in the area. During the dry season (June to December) rain seems rarely to fall at night or in the morning; there is a very heavy dew, so that in the morning grass, shrubs, etc., are soaking wet.

The humidity of the air arising from the evaporation of immediately fallen rain, the neighbouring swamps, rivers, and backwater, is very considerable, and generally approaches the saturation point. The atmosphere is often particularly stifling about five to seven p.m., when the air is quite calm. The afternoon rain is ushered in with a squall of wind.

From what has been said it may be gathered that it is rather the brainwork, combined with a considerable amount of monotony of climate and employment in an enervating climate, without much chance of recreation, that tells upon the health

* *Parà Medico*, I, No. 4, p. 112.

and vigour of Europeans, and makes comparatively frequent sojourns in more temperate climates advisable. With solely the uneventful and unworried mode of life in the forest, away from the cares and anxieties of commerce and civilization, the conditions are probably more favourable for prolonged residence in the Amazon valley. Thus, as an isolated instance, I may mention meeting R.H., an Englishman, now eighty-five years old, and fairly hale, who resides away in the forest several days canoe journey from Manáos, and whose last visit to cooler climates (England) occurred in 1847.

The general maintenance of health and energy would be enhanced by the establishment of fresh, or the improvement of existing means of transit, whereby better facilities for recreation would be afforded. Further, the welfare of European residents would undoubtedly be increased by an annual holiday trip for a few weeks, for instance, into a fresher climate, and change of scene and diet. At present, apparently, there is no definite system of holiday, so that in this respect the clerk in Parà is less fortunate than his brother at home, although he is exposed to a far less favourable climate. How far the towns on the seaboard of the northern Brazilian coast would be suitable for such a purpose, were good accommodation available, cannot be said without personal experience. Probably the change of surroundings would be insufficient, and at any rate these places are not used for health purposes to any extent either by foreigners or natives. The nearest place which seems to be suitable is the island of Barbados, which is a four-day voyage from Parà, and is not infrequently called at by the steamers on the service between New York and Parà. However, the quarantine board of the island impose a period of fourteen days quarantine—a period which seems to be fixed as a 'useful period for all infective disorders.'* This regulation necessitates a sojourn of ten days at the quarantine station (Pelican Island) and practically cuts off the use of Barbados as a recuperating station for the Amazon region. A little more freedom in rational framing of regulations, so that some distinction were made between immunes and non-immunes, and a limitation of detention to the latter class† for six or seven days, would redound to the mutual advantage of the island, and the residents on the Amazon.

Mortality. At the present time the death rate, etc., are calculated on a supposed population of 100,000 inhabitants in Parà; it would appear that this estimate is

* No distinction from the yellow fever point of view into 'immunes and non-immunes' is recognized by this board, although the classification has been found useful in the United States, into which immunes are allowed free entry without a detention of a period to complete five clear days, which is exacted for 'non-immunes.' Again the period of fourteen days is far beyond the limit of the incubative stage of yellow fever, which at most does not extend into a seventh day. Although small-pox is apparently also feared, no particular attention appears to be paid to whether persons are vaccinated or not. During my passage up to New York the vessel was loaded with sugar in quarantine. This consisted in taking a gang of labourers on board to stevedore, and keeping them until the next day, so that if any infected and infecting condition obtained upon the vessel, these labourers were exposed as much as possible to infection. When the loading was complete the men were taken directly ashore and allowed to distribute themselves to their homes. Much red tape is also employed in the signing of 'permits' to land and not to land labourers. This record may be of interest to the historian who wishes to see the amount of uncommon sense which was displayed in quarantine practice at the commencement of the twentieth century.

† I should be inclined not to consider a recent convalescent as an immune until about six weeks had passed since his being taken ill; since, apparently, a sort of secondary attack may sometimes occur about a month after the original attack.

rather too large for the city alone. Dr. AMERICO CAMPOS[1] quotes the figure 29,121 as the population in 1872, in 1896 it had risen to 60,218 ; by estimate from these figures the population in 1900 is worked out as 75,089 for the city alone, and 101,619 for the city and suburbs and a number of neighbouring places ; this last figure becomes 133,000 when another mode of reckoning is adopted. The deaths agree in number with the official figures of the interments in the city cemeteries, so that the larger figures should probably not be taken into consideration for estimating the mortality rate of the city itself. During the five years 1895 to 99[2] 16,346 deaths were registered in the city, which, at the supposed population of 100,000, gives an annual rate of 32·69 per thousand inhabitants. That this is much too low is probable from the accredited expansion of the city, and if we take an estimate from the above population figures of 60,000 in 1896, and 75,000 in 1900, the death rate works out at about 50 per thousand. The following gives the extreme ends of the period :—

In 1896 there were 2,492 deaths :	at population of	60,000 = 42·2	per thousand.
	„ „	81,000 = 30·7	„ „
In 1899 there were 4,806 deaths	„ „	100,006 = 48·	„ „
	„ „	133,000 = 36·	„ „

In 1900 the distribution is :—

1st three months	1076	deaths.
2nd „ „	1288	„
3rd „ „	1270	„
October	333	„
November	348	„
December	353[3]	„
Total ...	4,668	„

at population of	75,000 = 62.2	per thousand.
„ „	100,000 = 46.68	„ „
„ „	133,000 = 35.0	„ „

Even taking the higher figures for the population, the figures are by no means satisfactory, and so far as death rate is a gauge, the general health of Pará cannot be considered in a very enviable position. Perhaps a certain allowance might be made for the deaths of recent immigrants, amongst whom there must be a considerable number of deaths from yellow fever, which would affect the death rate as an index of the health of the acclimatized and prolonged resident. Again, a certain number are accountable by deaths of rubber cutters, who have contracted their fatal ague away in

1. *Pará Medico*, Dec., 1900.
2. A. Campos. *Pará Medico*, Jan., 1901, p. 68.
3. Average from Nov. 348, and Jan. 358, there being no figures to hand for the month itself.

the forest, and come to the city to die. Out of the total of 2,364 deaths in the first six months of 1900 (*loc. cit.*), 1,042 are ascribed to infective diseases, including malaria, yellow fever, smallpox, etc., which are not separated.

In judging these figures some comparison is desirable with other places. It is not fair to make a contrast between figures obtained in tropical places and those in temperate climes. Perhaps the fairest comparison may be gained by taking the statistics of British Guiana[1] as a place where the climatic conditions are not very dissimilar, and their geographical position not remote from one another. The temperature (British Guiana) is given as varying between the limits 88·3 and 70·5; the humidity 77 to 83 in 1900. The death-rate given for 1899 is 29 per thousand, and in 1900 it fell to 26; the population estimated at 294,943. It may be remarked that yellow fever does not appear on the list, and has been effectually stamped out for some years; also smallpox only accounts for one death; tuberculosis forms the largest item with 294 deaths, and of acute diseases dysentery comes next with 85. For incidence malaria is highest, but the deaths accounted to it are not so large.

It will be seen then that the mortality rate of Parà does not compare favourably with that of British Guiana; moreover, not only is there room for improvement but improvement should be an actual possibility.

Turning to the child mortality in Parà, of which there are some figures forthcoming,[2] between the ages of 0–5 years for the two years 1898-9, we find 824 and 1,527 deaths respectively; more than half the deaths occurred during the dry season in each case. Out of the grand total of 2,997, infective diseases account for 749, *i.e.*, 'malaria' 545 and other diseases 204. In the light of the recent observations on the meningeal form of the fever in yellow fever in children[3] the figures under the heading 'Molestias do apparelho encephalo-rachidiano e orgaos dos sentidos,' which amount to 229 may be of interest; Dr. CAMPOS says that only three children died of yellow fever during the biennial period. Measles accounted for 123, the remainder being due to smallpox, tuberculosis, whooping cough, diphtheria, and dysentery.

The percentage mortality of the total deaths of all ages is given at thirty-nine per cent. in 1898, and thirty-five per cent. in 1899.[4]

Merely as giving a suggestion of the relative numbers of deaths due to ascertained recognized specific causes, the following figures are quoted from Dr. CAMPOS' summary of the deaths in January, 1901,[5] when for the first time some classification, under different causes, was introduced in the tables.

1. *British Guiana Medical Report* for 1900; printed for Colonial Office.
2. *Parà Medico*, pp. 59 and 60.
3. Azevedo Sodré and Couto: *Nothnagel. Sp. Path. u. Therap.* Bd. V Theil IV, Abth II, p. 160.
4. *Ibid*, p. 34.
5. *Parà Medico*, February, 1901, p. 101.

The total deaths for the month were 358, or a proportion of 35·8 on the estimate of a 100,000 population. Some of the diagnoses given can hardly be given in English, but the style of diagnosis and its uncertainty in some of the headings may be judged of :—

Disease	Deaths
Impaludismo (malaria)	8
Cachexia palustre (malarial cachexia)	15
Febre intermittente (Intermittent fever)... ...	4
Febre palustre* (malaria)	5
Febre remittente typhoide (?)	1
Febre biliosa*	3.
Febre typhica	2
Accesso pernicioso*	6
Polyneurite palustre	2
Febre amarella (yellow fever)...	31
Tuberculose pulmonar	23
Variola	15
Beriberi	1
Dysenteria chronica	1
Lepra	1
Angina diphtherica...	1
Angina croupal	1
Tetano traumatico	2
Total ...	122

The following remarks are derived from conversations with the local physicians and occasional visits to the general hospitals, etc. :—

Malaria is dealt with elsewhere so that here it may be noted only that the determination of the presence of the malarial parasite, is practically a perfectly unused mode of diagnosis. A good many of the cases are imported from the islands and other rubber districts. Bronchitis when diagnosed is often ascribed to malaria.

Tuberculosis is one of the chief scourges of the place, as the above figures indicate, the small dark houses, the universal and free spitting everywhere and anywhere, and the fine siliceous dust in dry weather may be regarded as contributive factors. I was informed that certain old sage negro women were in the habit of applying sputum to the breasts of mothers as a means of child murder.

Variola ('Bexiga') is also one of the banes of the place. Much effort has been made to secure vaccination, but the practical difficulties are very great and only a small proportion are thus protected ; revaccination is probably still more rare. An isolation

The headings marked * are sometimes synonymous with yellow fever.

hospital (Sao Sebastian) was opened on February 14, 1900; from this date to the end of the year no less than five hundred and eighty-five patients were admitted. Of these one hundred and seventy-three died; but it is noted[1] that many of the deaths were due to other causes than variola (*e.g.*, 'malaria, beriberi and cardiac, and renal complications'), and during our stay we came to learn that one of the devoted nursing sisters at this hospital succumbed to an attack of yellow fever. Varicella apparently also occurs.

Measles ('sarampo') is not uncommon, and epidemics occasionally occur; during our stay we saw a few cases. Pertussis is also not uncommon. Ordinary and severe 'colds' in the 'head' are frequent.

Beriberi occurs, but is not very common; a few cases were seen.

Yellow Fever ('Febre amarella') was introduced into Parà[2] from Pernambuco by means of the vessels 'Pollux,' which arrived from the fever-stricken port on January 24, 1850, and the 'Pernambucana,' which arrived from the same port a few days later. Two sailors of the former died on the last day of the month, and on the next day three sailors from the latter died; no further deaths are recorded during February which is of interest; in March there were forty-one, and April two hundred and sixty-nine. During the year three-quarters of the population were attacked, which suggests that fatal epidemics in previous years were due to other causes, as variola, etc. Thus a total of twelve thousand persons out of the total population, estimated at sixteen thousand; the deaths ascribed to the yellow fever were five hundred and six from January to July, deaths due to other causes being three hundred and four; altogether corresponding to an annual rate of one hundred and one per thousand. Persumably the deaths due to yellow fever were more numerous than was admitted, owing to concealment, so as to obtain interment in churches (of which there were one hundred and eleven during the period) and consecrated ground.

Soure and other places in the neighbourhood apparently were infected very soon, but no doubt from the slight amount of commerce up the Amazon the disease was not carried along this waterway till a much later date. Manáos was severely stricken during recent years, chiefly, no doubt, through the importation of numbers of non-immune labourers. From accounts it appears that the infection has been spread up as far as Iquitos, two thousand miles or so up the river.

Apparently the fever has remained to stay in Parà ever since. The local boast that this and other bad illnesses are imported and not national is not a sufficient excuse for not stamping it out.

There are some indications of the prevalence of the fever in the city during recent mouths by the entries of patients and the death roll at the isolation hospital,

1. *Parà Medico*, I, p. 21
2. A. Vienna, *Parà Medico*, I, p. 35.

'Domingos Freire.' This was opened on the 29th of April 1900, for the reception of patients.

	Month	Admissions	Deaths
1900.	To end of May	83	33
	„ June	94	42
	„ July	87	42
	„ August	85	30
	„ September	56	20
	„ October	34	12
	„ November	31	9
	„ December	44	11
1901.	„ January	51	21
	„ February	45	10
	„ March	29	5

Amongst these cases are a small proportion due to other diseases, but the majority are due to yellow fever. The figures, however, are merely an indication of the amount of the disease that was prevalent at the time, for there is no compulsory isolation, thus many cases remain distributed at their own homes ; most of those that found their way into the general hospitals were transferred, but not always ; lastly, there are a number of cases which are not recognized, or are called by other names.

Leprosy cases, when recognized, are sent to an isolation hospital out in the forest at the back of the S. Isabel region. The patients seen were mostly rather advanced examples of the disease, and were one hundred and eight in number at the time of my visit. The number corresponds to 0·5 per thousand of the population of the whole state. The Rio Tapajos by repute is the chief centre of the disease ; probably not more fish is eaten there than in other riverain places.

Venereal complaints are common. Gonorrhoea is very frequent, and I was told that the majority of the female patients who applied for treatment at the general hospital were either suffering from some form of this or from phthisis. Amongst the patients at the yellow fever hospital we did not notice much syphilis, or signs thereof.

Diphtheria is quite rare ; an occasional case occurs, but it appears that the disease does not tend to spread. Whether this is due to an absence of the conditions which cause its spread in other climes, or whether it exists in a modified and unrecognized form of tonsillitis, cannot be said. The children on their way to school may be seen carrying their little bottle of ink and pens, slates are probably too expensive an exotic luxury.

Scarlatina is another disease which is said to be practically unknown ; again, either the climate, etc., is not suitable for the extra-human life of the causative agent, or else the conditions necessary for its spread from individuals are absent.

Typhoid Fever and Dysentery are also very uncommonly met with or diagnosed as a local product. Such water supply as there is seems to be fairly well protected from contamination at the source.

Yaws and Lobar Pneumonia are not recognized.

Tetanus is not uncommon.

Rabies is said to occur now and again. Lately steps have been taken to undertake the preparation of spinal cords for Pasteurian treatment. Hitherto, when required, the material has been imported. Curiously enough, the more effective and economical step of clearing out the more or less ownerless and scavenging dogs has not been taken. Numbers of dogs, usually in a disgusting state of mange, covered with ticks, and their feet full of jiggers (*Sarcopsylla*), are seen about the town, which might well be destroyed, and would be calculated to make the disease common, when it is introduced.

(I understand that Manáos was once cleared of stray dogs by the cruel method of transporting them over the river to an island).

For practical purposes the acute diseases at Parà, which are the most dire for the place and region, are malarial fevers for which a careful survey of the *Anopheles* breeding-grounds is desirable ; so far as they were seen, they ought to be easily dealt with in the precincts of the city. Smallpox which is already being attacked by vaccination and isolation. Tuberculosis, which requires the introduction of more hygienic personal habits amongst the people. Yellow fever, which requires the careful and early recognition and notification of the cases, their early and compulsory isolation, and the destruction of breeding-grounds (casual waters, cesspools, rain gutters, etc.), for mosquitoes about the houses. Filarial disease has not been mentioned above ; a few cases are seen of obvious lymphscrotum, and a few cases of elephantiasis about the town. The protection of the general hospitals by means of permanent ' bars ' in the windows ; doorways to keep out mosquitoes, and so prevent these places from being a sort of filaria exchange is all that need be said, except that it would be advisable for persons to avoid having infected persons living in the houses. It may be noted that one of the mosquitoes caught in one of the hotels was found to contain an embryo filaria.

It seems that the undertaking of any of these points would be more profitable than a considerable outlay against more or less hypothetical rabies, and conduce to the improvement of the local sanitary condition.

It remains to say a few words concerning the hygienic steps taken by human interference apart from the natural conditions which obtain.

Water Supply. The supply of water is bad, from the points of view of quantity, quality, and the possibility of contamination. For more than two years the water has not been sufficient in quantity, partly owing to the inadequate size of the mains and the pumps ; thus in one house in the city it was not possible to get a shower

bath on the ground floor after about eight a.m.; at the hospital, Domingos Freire, no water came through the pipes after eleven a.m. In many houses private pumps and cisterns were arranged so as to ensure a supply through the day. As regards quality, it may be noted that the water as it flows from the tap is frequently very full of brown sediment, so that it is quite opaque; dead flies, mosquitoes, and their larvae have also been encountered in the water flowing directly from the tap. When the water supply ceases and the tap is turned there is strong insuction of air giving the possibility of the introduction of other things. The amount of water is given as over 1,000,000 litres per diem,[1] that is ten litres per head per day. Especially in outlying districts local wells or springs are used. The community generally is wasteful, and much water finds its way in watering gardens, etc. Public standpipes are provided about the city so that the poor can obtain water free of charge; in houses where it is laid on it is taxed by meters. The gathering ground is a charming collection of springs at Utinga well away from the city beyond the Marco da Legua. We were promised an official visit of inspection of the new works that are being put in, but, for some unaccountable reason, it never took place. Except one stream, passing down in close proximity to the pumping station, and in which people bathe, wash clothes, and which is crossed by a public footpath, and liable to pollution from several houses in its proximity, and of which we were unable to determine the eventual fate of the water, the springs and streams seem well sheltered from pollution. New works are being pushed forward, including large mains of nearly one metre diameter; naturally this is slow work, and the temporary laying of a small subsidiary main for immediate purposes was not adopted, so that the water supply is not likely to be very adequate for some time longer. It may be mentioned, in passing, that these large pipes for the mains have been lying about in most indescribable filth in the roadways, etc., for some time, others have been employed as dormitories, so that when the new service is instituted persons should be more than ordinarily careful about the filtration and the boiling (if the servants are sufficiently reliable) of water for consumption.

Sewerage. Some part of the city is supplied with drains, mostly at any rate the mains are old brick constructions, and probably not free from faults. The amount of water available for flushing out is quite insufficient, though the rivers afford an unlimited available quantity. It seems hardly worth considering alterations until there is sufficient water available for efficient water carriage. Probably the major part is served by cesspools; these are such that in many cases the watery constituents are said to filter away into the sand, leaving a very slight amount of solid residue; those which I saw, however, were full of water, and formed an abundant source of the *C. fatigans* mosquito.

1. *The State of Para*, 1893, p. 113.

For surface drainage many of the outlying streets are unpaved, and consequently are liable to be full of puddles; here a system of excellent side gutters of cement has been put in, and thus much of the rain-water is rapidly carried off. These are being extended and the lie of the land is sufficient to give gradients in most places; naturally some of the older gutters are more or less obstructed in parts by the rubbish, and hosts of mosquito larvae are to be found in the retained water; but on the whole they are kept clear, a condition which is aided by the tremendous flushing which occurs during a rain shower. The sandy nature of the soil assists greatly in the natural destruction of gnat-breeding puddles.

The rain gutters which take off the water from the roofs requires serious consideration if the city is to be freed from mosquitoes. They are frequently fixed so as to be almost horizontal, well supplied with bends, corners, and dead-ends, so that there is every opportunity for retaining water from the constructional point of view; more than this, a walk along the streets will show that many are obstructed with growing plants or trees. There is quite an opening for justifiable municipal legislation to deal with the necessity of keeping all such gutters free from obstruction. Also when they are put up, since they are frequently inaccessible, or only accessible with difficulty, they should originally be put up with a considerable gradient, so that they will tend to clear themselves out and give no chance of stagnation. Moreover, downward pipes should be provided at acute turns. The water gutter is a serious question in Pará since the almost daily showers in the dry season tends to keep them constantly filled with water if there is obstruction.

Rubbish destruction. In their praiseworthy efforts to improve the sanitation of the city, a system of collection and destruction of household rubbish has been instituted by the authorities. In the evenings householders deposit the rubbish of the day in the gutter opposite their houses, and if these are on the track pursued by the collecting carts, as the principal streets of the city, it is collected and carried away to the furnaces. Recently some new furnaces have been erected, which should be capable of doing the work in an economical manner; unfortunately, however, the nature of the rubbish to be destroyed does not seem to have been adequately studied before the furnaces were designed, so that on trial they were not found entirely satisfactory. In the more outlying districts the rubbish remains and the effluvia are unpleasant. The mode of cartage is clumsy, and would be much facilitated by the use of some of the tramway tracks and extensions thereof. The sweepings from the stables of the tramway company (Compania Urbana) are carried out beyond the city to the grass fodder growing district at Sacramento; in the neighbouring forest are some choice spots, where the carcases of dead mules and oxen are dumped from time to time; the latter are to be dealt with by cremation at the destructor furnaces.

Living houses. It cannot be said that the general plan of the houses is suited to the climate; even in comparatively good houses there is absence of verandahs and good

arrangement for ventilation. The poorer class mostly live in dark dens in the city not arranged for through ventilation ; in the outskirts there are some terraces of cottage quarters, though as one proceeds out detached palm-thatched huts are the rule. In the latter the people keeps things clean and tidy, with the exception of free expectoration on the dried mud floors ; but more within the city the quarters are often very filthy. As a race the Brazilian is of cleanly habit, so far as personal washing and linen go. The almost universal use of the 'rede' (a kind of hammock) instead of bed for sleeping may conduce to the reputed absence of bugs and the comparative rarity of fleas, although these must be constantly imported by the indigent immigrant from the slums of Portuguese, Spanish, and Italian towns.

Hospitals. Lastly, a word must be said about the hospitals. A large general hospital, Santa Casa de Misericordia, has been built in the Umarizal quarter of the city. The large wards seem airy, well kept, and clean. The basement is also used for wards, and though well kept the conditions of light and air are not so good. Copious water supply is ensured by pumping up into large storage tanks. There is also an elaborately decorated and furnished committee room, the expense of which might well have been foregone to admit of the introduction of more immediate necessities. The chief fault is one of omission, for there is no provision for keeping out mosquitoes ; large numbers of blood filled mosquitoes are to be found any day in the dark corners ; there can be no question that all window spaces and doorways should be protected with permanent wire gauze nettings. In a hospital it is not possible or advisable to have individual nettings for each patient ; with the movements a certain number of gnats would be almost certain to effect an entrance, these could easily be dealt with by inaugurating a brigade of convalescents armed with small 'butterfly nets' ; perhaps, in certain instances, such as malarial and filarial cases of diseases, the patients might be kept in a specially guarded ward ; the same would be done in yellow fever suspects. At the same time all breeding places for mosquitoes in the neighbourhood ought to be kept under survey. With such improvements in many ways the hospital may well bid as a model hospital for tropical cities.

Also under state or municipal control are the isolation hospitals for yellow fever and smallpox ; the latter was not seen, and the former is deserving of praise in its cleanliness and brightness. Better water supply arrangements are urgently needed, and what has been said of making the Santa Casa mosquito proof, can only be repeated here. The nursing is done by the sisters of an Italian sisterhood (Sta Anna) in all these hospitals ; the people, perhaps, hardly realize how much they are indebted to the devotion and care of these good women, who come out at considerable personal risk to minister to the sick, and not a few have added to the death roll, chiefly of yellow fever. The isolation for leprosy (Asilo dos Alienados) is situated away in the forest, and consists of a number of huts and houses with a common refectory, etc. There is also an asylum for lunatics out at the Marco da Legua ; this was not visited,

it is said that there was a severe visitation of beriberi at one time. Besides these there are other hospitals such as the 'Portuguese' and the Ordem III of S. Francisco.

Lately a quarantine station has been put in working order at the delightful little island of Tatuoca, about twenty miles down river from Parà; it is supplied with disinfecting apparatus and accommodation for patients and detention of suspects. Before this was opened the nearest quarantine station was that of Ilha Grande, at a distance of about two thousand miles. Ghastly as it may seem vessels have made this journey at the bidding of the panic stricken authorities; now that this has been rectified by energetic pressure no more need be said on the matter.

Mosquitoes

Remarks on the hygiene of a place in the tropics would not be complete without some reference to dealing with the mosquitoes. In some houses visited, they are so numerous that even poorer people make use of mosquito nets for sleeping under; this, however, is not general. It appears that old inhabitants and natives are by no means insusceptible to the annoyance of the insects, still on the whole they do not trouble to protect themselves; nor are any steps taken to treat the breeding-places of the insects.

English residents with whom I have spoken say 'what is the use of my dealing with the precincts of my house unless my neighbours do the same, for I shall get so many gnats from next door that my own endeavours will be useless for my own comfort.' This is, no doubt, true to some extent, and really forms the key to dealing with the mosquito question, namely, that to be of real use organized and combined and continued attacks upon the insects must be made. Dilettante destruction, or temporary energy, here and there, will probably never be of any real service. There is much that might be done in Parà in this respect, and probably the attack on breeding-places is the most practical method of dealing with the matter. The construction of the houses is not very favourable for fixing up permanent wire gauzes, such as one sees in the United States, and which are being introduced into other regions.

Besides the cesspools and rain gutters, which have been mentioned elsewhere, the carelessness of people leaves all sorts of neglected collections of water about the houses, wash tubs, odd tins, etc. (In Cuba, the Americans deal with these by fining householders for having unnecessary and unguarded water accumulations on their premises).

The flushing tanks of water-closets which are in constant use do not seem to be great breeding-grounds, unless they are left unused; still there is no harm in having them covered with gauze.

These sites, with possibly the main sewers which are constantly fed from gutters, etc., filled with larvae, seem to be the chief breeding-places about the paved part of the town ; the gardens, often with fountains and circular water troughs round the plants for keeping off the destructive Sauba ant, also require attention for they form a fertile source of *S. fasciata.* In the unpaved parts, naturally, there are many odd pools from time to time, those of natural origin from the configuration of the ground, and those due to obstructions in the roadside channels, especially the unconcreted ones. The pools in which *Anopheles* larvae were found, as mentioned elsewhere, are eminently adapted for treatment by filling up on account of their small and shallow nature ; a complete survey of these is required. Living specimens of the larvae and adults of the *Anopheles* were shewn to many of the local medical men and others.

Experiments were intended, but never carried out owing to stress of other things, to try the culicicidal effect of poisonous plants in the local flora. About Parà are numerous examples of the Solanaceae (for instance, the 'jurubeba' *Solanum grandiflorum*), and if means like the leaves or other parts of common local plants will act, when placed in casual waters from which drinking supplies are not obtained, by killing contained mosquito larvae, a simple and economical warfare can be waged on the insects without much exertion.

A few words may be said about mosquitoes on the ships about Parà. It is said by captains that mosquitoes only commence to come on board when the lighters which are used for the discharge of the cargo are brought alongside. Seeing that the anchorage for the large ships is some two miles below the city, and the lighters lying about the neighbourhood of the city are brought to wharfsides for discharge, they are a means of bringing city mosquitoes to the ships. On examination, several of the large barges (which are covered with a rainproof metal cover) were found to harbour a certain number of the insects, both *S. faciata* and *C. fatigans* were found in the adult condition and a few larvae of the former in the bilge water ; but these lighters had recently been cleaned up and painted ; open lighters are also used, these were seen to contain abundant rain water and tar and oily material from the coal for which they are used ; no larvae were found in them.

During my trip up to Manáos, indiscriminate collection of all and any mosquitoes that could be found on board was made. Although a number were collected it was not until after anchoring at Manáos and the lighters came alongside that the species *S. fasciata* was taken. It appears that the method of discharge by means of lighters may be almost as risky for the importation of mosquitoes infected in the city, as if the vessel was actually brought to the wharfside. The only recommendation that seems likely to be effectual would be to fumigate the lighters some time before they were brought alongside by burning sulphur within them.

A certain amount of breeding of mosquitoes may occur upon the vessels; thus one captain told me that he once discovered larvae in the water tanks. The telegraph ship which has been many years upon the Amazon was examined; very many *S. fasciatus* and some other gnats were seen and taken. Besides it was found that there were abundant larvae of *S. fasciatus* in the bilge water; some permanganate of potash had been put down with a view of killing them, but the quantity was probably much too small and most of it soon decomposed; the trial of a small quantity of kerosene oil was suggested as a more likely means. In vessels such as this which remains long on the river as well as those which are only a short time, there ought to be provision of netting to fit portholes, doorways, lights, etc., so that at any rate a certain amount of protection and comfort might be obtained.

IX. ODD NOTES

A. On the Etiology and Treatment of a Skin Eruption known as 'Prickly Heat'

A form of irritating acute skin eruption is widely spread in Parà; by the English-speaking folk it is called 'Prickly Heat,' and so far as the description goes it seems to be identical with what is commonly understood by the term.

The chief points to be dealt with at present are :—

1. Its infective nature.
2. The living organism associated with it.
3. The mode of treatment and cure.

The infective nature could clearly be traced by the course followed upon myself. On the ulnar aspect of each wrist, for weeks after arrival at Parà, I was troubled by what I took to be an unusually swollen and long-lasting gnat bite. My attention was especially attracted to that on the right wrist a few days later by the appearance of an irritating patch of redness, with small vesicles about the middle of the forearm, and also at the same time a similar condition had spread about the neighbourhood of the original papule. I found that the sites corresponded with the points of contact of my wrist and forearm with the edge of the table during the use of the microscope; and it appeared clear that the patch on the forearm was due to implantation of the causative material from the wrist to the table, and so to the forearm. Not long afterwards a patch appeared on the front of the lower part of the chest, which I found was a common point of contact for the patch on the forearm. Later observation shewed that direct infection by local contact could occur as from a spot on one side of the bend of the elbow or fold of the axilla to a corresponding contact point on the other side. It seemed probable also that a certain amount of spreading might be due to rubbing or scratching 'without antiseptic precautions.' To cut matters short, before the condition was properly dealt with it had spread more or less universally. It may be added that there was only a slight amount of spreading in the near neighbourhood of the initial lesion on the left hand.

My late helper and colleague, Walter Myers, also suffered in the same way about the same period, but except that he was inclined to attribute the initial lesion to a gnat bite I am not aware of the course of the distribution.

Although suspicion attached the original inoculation to the bite of a gnat, which if this were the case, would almost certainly have been *Stegomyia fasciata*, this was by

no means proved. It may quite well have been due to handling the yellow fever patients, many of whom were affected. This is a point which can only be determined by careful watching in an individual who has never before been affected on a first visit to tropical regions.

The lesions seen at the very earliest consist of a patch of inflammatory reddening with a tiny vesicle at its middle; the vesicle enlarges, but generally remains quite small; the contained fluid is at first clear, but later may become turbid and finally purulent if it persists and does not disappear. Where there has been local spreading a considerable area of skin may be reddened and scattered about upon it are numbers of the vesicles; these are generally more minute than when a single isolated vesicle develops. In distribution they are between the hair follicles, and presumably are due to the involvement of the sweat glands. Occasionally, however, they may be close to the hair follicles, and these sometimes appear to get involved. Presumably, at the moment when the vesicle becomes tense, a sharp, intense sensation is produced, and the inclination to rub or scratch is very great. Rubbing or scratching, however, rather tend to increase the irritation. After a time the local condition subsides spontaneously, but it may reappear at the same site on a future occasion; meanwhile other areas are in the acute stage.

Microscopic contents of the vesicles. With the aid of some squeezing and a very fine capillary tube, the contents of the vesicles can be removed and examined. When the vesicle is not too far advanced the fluid is clear, and is generally found to contain a few red blood corpuscles but no leucocytes; at a later stage the leucocytes appear in greater or less numbers and give the purulent character. What attracts the attention at the early stage, before the advent of any or at any rate many leucocytes, is a number of small bodies endowed with active amoeboid movement. Their protoplasm is more refractile than that of the 'polynuclear' leucocyte, and contains a small number of granules of a highly refringent character. The changes in shape of these amoeboid bodies are rapid without artificial heating of the slide at the ordinary afternoon temperature (27°-30° C), the pseudopodia being generally comparatively blunt and rounded. The accompanying sketches shew some changes in shape, which occurred within the space of a minute or two (Fig. 3).

When the suppurative change has commenced large numbers of polynuclear leucocytes are to be seen, either entire or more or less disintegrated; micrococci in pairs or in groups are also present in variable, generally small, numbers. Active amoebae, however, are then rarely found, but there are some globular bodies which would correspond in size to and which are possibly of the nature of encysted amoebae.

The abundance of the amoeboid bodies at the earlier stages and the absence of micrococci or other bacteria at this time make it probable that the formation of the lesion is concerned with the presence of the amoebae, the later invasion and suppuration, when it occurs, being caused by the micrococci or other bacteria.

In regard to the pathology of the condition, the circumferential redness is suggestive of some chemical as well as of a mere mechanical action ; at the same time there does not appear to be any marked effect upon general health.

These observations were made upon the contents of vesicles occurring upon my colleague and myself.

Treatment. It has already been observed that the lesions in one place resolve spontaneously, whether the active agent merely lies latent or actually dies, so that reinfection is necessary for the same area to be reinfected cannot be answered.

The adult natives do not appear to be troubled, but the small babies are often seen with what appears to be an identical condition. At the same time, individual immunity is not always acquired by long residence, as I met with a gentleman who had been about Parà for more than ten years, and who said he had never been so troubled with prickly heat before, and certainly he was pretty well covered with the lesions.

A considerable number of different applications were put to the trial. Those which were found useless may first be mentioned and disposed of. The 'palliative' applications of toilet powder, of boracic acid in powder or solution, lysol (one per cent.), carbolic acid (five per cent.), alcohol, permanganate of potash, sulphurated potash (five to ten per cent., which is quite effective for dhobie itch), were found to be perfectly useless ; they neither relieved the itching nor did they cure the condition. Numerous shower baths, whether followed or not by a sponging with weak permanganate of potash and spontaneous drying, likewise did no good.

The two applications which were found of service were iodine and corrosive sublimate. The former was used in the form of tincture diluted with spirit so as just to stain the skin well ; this has the disadvantage of staining the skin and also marking any starched linen temporarily. The corrosive sublimate was used in solution of about 1 : 500 to 1 : 1000 in spirit and water, in water alone or in water glycerine and spirit (the idea of the glycerine being to prevent irritation by the drug). The first of these seemed to be the best, though its superiority was not great over the others, for plain aqueous solution acts perfectly well. The mode of application was to rub well with a pledget of cotton-wool well wetted with the solution ; the next day the red inflamed areas have disappeared, and the sites of the more deeply infected follicles have a brownish colour instead of a bright pink, and on rubbing they are not so irritable. Two or three applications may be required to get rid of the deep infections, and it seemed more satisfactory to go over considerable areas at a time. The most deeply affected follicles are the most difficult to eradicate entirely, and some were treated by expression after the manner that the old housewife extracts a wasp sting by means of a key barrel, with the pressure of the end of a small glass tube, in which a small quantity of the antiseptic solution is held by capillarity. This, which is an effective mode of evacuating ordinary suppurating follicles also, is not altogether a pleasant

proceeding, and a doctor might be advised to try on himself before he subjects his patients to it. Refractory follicles may be touched with strong iodine tincture.

Corrosive sublimate has the disadvantage of being unpleasantly poisonous to leave about in lay hands for promiscuous application, so that some less dangerous material or form of the material would be advisable for practical purposes. As a suggestion, which gives promise of being well worthy of trial, I may mention the antiseptic soaps which are used for obstetric and other purposes, or more precisely those which contain mercurial salts (generally the iodide, I believe). A cake of such a soap would not be so objectionable on the score of its poisonous properties. Naturally, for portability, a cake of soap does not compare with a few tabloids of Hydrarg. perchlor : a small portion of one of which will do a good deal. Enquiry may reveal some more preferable protoplasmic poison ; formalin and salts of copper were not tried.

It is not without interest to observe that the ordinary suppurating follicle with staphylococci is readily cut short, with carbolic acid (*e.g.*, sat. sol.), whilst the prickly heat is not affected as would be probable if the skin staphylococci were the cause.

Summary. The condition of ' Prickly Heat ' studied is infectious by contact ; it is associated with the presence of active amoeboid bodies ; it is curable by means of applications of corrosive sublimate, and, probably, other protoplasmic poisons.

B. Drepanidium in the Toad

All the smaller toads which we examined at Pará (*i.e.*, about the size of the ordinary English toad) were found infested with a species of *Drepanidium.* Two main forms of blood parasite were found, in the red-blood corpuscles one corresponding to the ordinary drepanidium and the other to Labbe's *Dactylosoma.* The former seemed to multiply chiefly, if not solely, in the internal organs (liver), the latter inside the circulating red-blood corpuscle. Once inside a red-blood corpuscle, it appeared that the drepanidium form did not leave it within the body of the toad ; for by fixing large quantities of blood from the heart immediately with sublimated saline solution and centrifugalizing we never succeeded in discovering free drepanidia ; on the other hand, if the blood was examined without a fixative agent or centrifugalized with plain citrated saline, after a short while no endocorpuscular drepanidia could be found, all having become free. This is suggestive that the drepanidium may be destined for a life in a second host. This host is, in all probability, to be found in the ticks *(Ixodes),* with which almost all the toads found were infested. Examination of the contents of the ticks shewed curious cysts, evidently different from the curious nuclei of the tick's economy, varying in size up to about 60μ. It was noted that the movements of free drepanidia in the fluids from the tick's stomach were much more active than in the toad's blood ; appearances suggestive of conjugation were also seen. Owing to our yellow fever work the observations were necessarily fragmentary ; moreover,

we could not obtain uninfected toads for trial of experimental infections. Further details may be forthcoming from the examination of the prepared material, which is to be examined. The suggestion is that the depranidium form is the gamete which completes its development in the arachnoid host, whilst the dactylosoma is the endocorporeal permanent parasite of the toad, they were not seen to leave the corpuscle in material either from tick or toad.

An observation which may be of interest in the economy of tickborne diseases, for instance, in Texas cattle fever in which the young ticks are capable of carrying the infecting agent, is that a tick which had been left in a box laid eggs which had hatched out during my illness. The young ticks had eaten nearly all of the contained blood and organs of their mother. *If the tick stages of a parasite* (as drepanidium in this case) *were alive in the mother, this would form a ready mode of securing the continuity of the existence of the parasite; this would be especially important for the parasite in the case of a tickborne disease, for ticks usually remain upon a single host, and therefore would not be calculated to spread a disease from animal to animal.*

C. A. Trypanosome

A small bat (*Phyllostoma*) which could not be examined at once was placed in a gauze cage, and with it a specimen of *S. fasciata*. The next day the bat was dead and the mosquito full of fresh blood. This blood contained abundant trypanosomes, whose shape is quite different from the usual ones in rats, Nagana, etc. Too much *post-mortem* change had occurred in the bat for satisfactory examination, but there were some structures which suggested altered trypanosomes; one knows from Nagana how soon after death of the host changes ensue in the trypanosomes. Other bats were obtained but there was never leisure to examine them until death had occurred. Although often flagellates, coccidia like bodies, etc., were found from time to time in the eighty mosquitoes which were dissected, this was the only time that trypanosomes were found.

Other Animals

Blood examinations were made on a number of different animals. Only one out of about a dozen lizards (green ones and brown ones) showed endo-globular parasites. One small brown bird of the pigeon tribe was found full of Halteridium. A toucan and an agouti were negative.

In the island of Marajo, about the cattle ranches, horses, dogs, etc., are said to suffer from a disease, consisting of wasting and paralytic symptoms, called 'quebra brunda.' It occurs during the dry season, and by local repute the capibára (*capybarus*) are said to sicken when or before the disease is prevalent. We saw many cattle with abundant ticks; these were in a meagre and wasted state of health.

8. 1. 03.

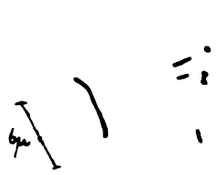


fig I.

fig II

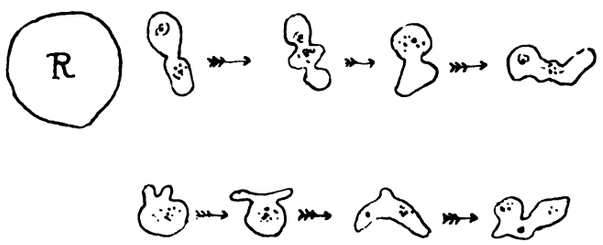


fig III

FIG. 1.—Group of 'small bacilli' from blood of 'typical bite.'

FIG. 2.—Two 'polynuclear' leucocytes from a preparation of a bite received at night about thirty hours before (mosquito—*C. fatigans*).

FIG. 3.—Sketches to show the changes in shape of two amoeboid bodies in the fluid from a young 'prickly heat' vesicle.

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